```
=>
=>
=> fil reg

FILE 'REGISTRY' ENTERED AT 12:12:41 ON 30 JUL 2004
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STRUCTURE FILE UPDATES:   28 JUL 2004  HIGHEST RN 718597-29-6
DICTIONARY FILE UPDATES:  28 JUL 2004  HIGHEST RN 718597-29-6

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> fil zcaplus

FILE 'ZCAPLUS' ENTERED AT 12:12:46 ON 30 JUL 2004
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FILE COVERS 1907 - 30 Jul 2004  VOL 141 ISS 6
FILE LAST UPDATED: 29 Jul 2004  (20040729/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 12:12:49 ON 30 JUL 2004
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FILE COVERS 1907 - 30 Jul 2004 VOL 141 ISS 6
FILE LAST UPDATED: 29 Jul 2004 (20040729/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> FIL STNGUIDE

FILE 'STNGUIDE' ENTERED AT 12:12:52 ON 30 JUL 2004

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jul 23, 2004 (20040723/UP).

=> d que l199

L182 (1) SEA FILE=HCAPLUS ABB=ON PLU=ON US2002-098644/AP,PRN
L183 SEL PLU=ON L182 1- RN : 169 TERMS
L184 (169) SEA FILE=REGISTRY ABB=ON PLU=ON L183
L185 (4) SEA FILE=REGISTRY ABB=ON PLU=ON L184 AND (C16H14N2O3S OR C17H14O4S OR C16H9F5N2O3S OR C16H14N2O3S)/MF
L186 (13) SEA FILE=REGISTRY ABB=ON PLU=ON L184 AND (C17H14F3N3O3S OR C17H12F4N2O4S OR C17H16N2O4S OR C16H11CLF3N3O2S OR C17H12F2O4S OR C16H13F2NO4S OR C17H14F3N3O2S OR C16H12F3N3O2S OR C17H14F3N3O2S OR C17H12BRFO2S2 OR C13H18N2O5S OR C16H13F3N4O2S OR C14H13N3O4S2)/MF
L187 (17) SEA FILE=REGISTRY ABB=ON PLU=ON L185 OR L186
L188 (40) SEA FILE=REGISTRY ABB=ON PLU=ON (123653-11-2/CRN OR 162011-90-7/CRN OR 169590-41-4/CRN OR 170569-86-5/CRN OR 177660-77-4/CRN OR 177660-80-9/CRN OR 177660-92-3/CRN OR 181695-72-7/CRN OR 185344-51-8/CRN OR 185344-55-2/CRN OR 195061-34-8/CRN OR 195065-56-6/CRN OR 195065-57-7/CRN OR 71125-38-7/CRN OR 80937-31-1/CRN OR 88149-94-4/CRN OR 93014-16-5/CRN)
L189 (57) SEA FILE=REGISTRY ABB=ON PLU=ON L187 OR L188
L190 (32) SEA FILE=REGISTRY ABB=ON PLU=ON L184 AND MAN/CI
L191 (30) SEA FILE=REGISTRY ABB=ON PLU=ON L190 NOT (39391-18-9 OR 80619-02-9)/RN
L192 (1373) SEA FILE=REGISTRY ABB=ON PLU=ON CYCLOSPORIN/BI
L193 (1403) SEA FILE=REGISTRY ABB=ON PLU=ON L191 OR L192
L194 (2) SEA FILE=REGISTRY ABB=ON PLU=ON (39391-18-9 OR 80619-02-9)/RN
L195 (120) SEA FILE=REGISTRY ABB=ON PLU=ON L184 NOT (L194 OR L193 OR L189)
L196 (6040) SEA FILE=HCAPLUS ABB=ON PLU=ON L195
L197 (1841) SEA FILE=HCAPLUS ABB=ON PLU=ON L189
L198 (14626) SEA FILE=HCAPLUS ABB=ON PLU=ON L193
L199 23 SEA FILE=HCAPLUS ABB=ON PLU=ON L196 AND L197 AND L198

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=> d que l100
L1             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  39391-18-9/RN
L2             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  80619-02-9/RN
L3               SEL  PLU=ON  L1 1- CHEM :      36 TERMS
L4         22401 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3
L6         12138 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 (5A) (?INHIBIT? OR ?RUPT?
                 OR ?BLOCK? OR ?DISABL? OR ?STOP?)
L7               SEL  PLU=ON  L2 1- CHEM :      10 TERMS
L8          4694 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7
L9          3004 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 (5A) (?INHIBIT? OR ?RUPT?
                 OR ?BLOCK? OR ?DISABL? OR ?STOP?)
L10         6670 SEA FILE=HCAPLUS ABB=ON  PLU=ON  IMMUNOMODULATORS/CT
L11        16528 SEA FILE=HCAPLUS ABB=ON  PLU=ON  IMMUNOSUPPRESSANTS/CT
L12         8836 SEA FILE=HCAPLUS ABB=ON  PLU=ON  CYTOTOXIC AGENTS/CT
L13         4356 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (PROLIFERAT? (L) INHIB?)/CW
L14            0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANTIPROLIFERAT?/CW
L15        58930 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANTI-INFLAMMATORY AGENTS+PFT,N
                 T/CT
L16        32725 SEA FILE=HCAPLUS ABB=ON  PLU=ON  INFLAMMATION/CT
L17          377 SEA FILE=HCAPLUS ABB=ON  PLU=ON  TRANSPLANT AND TRANSPLANTATION
                 /CT
L18        53343 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (LEUKOCYT? OR LEUCOCYT?)/CW
L19            0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (ANTILEUKOCYT? OR ANTILEUCOCYT
                 ?)/CW
L20        19595 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ?CYCLOSPORIN?
L21       177028 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L10 OR L11 OR L12 OR L13 OR
                 L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20)
L32          650 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6 (L) L9
L34          306 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L32 AND L21
L36          205 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L34 AND (AY<1997 OR PY<1997
                 OR PRY<1997)
L37           88 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L36 AND (MIX? OR ?MIXT? OR
                 ?COMBIN? OR ?COMPRIS? OR ?COMPOS? OR COMB OR COMPN OR DUAL OR
                 ?SYNERG? OR BLEND)
L38           75 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L37 AND (L10 OR L11 OR L12 OR
                 L15 OR L20)
L39            4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L38 AND L20
L45 (          1)SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2002-098644/AP,PRN
L46              SEL  PLU=ON  L45 1- RN :     169 TERMS
L47 (        169)SEA FILE=REGISTRY ABB=ON  PLU=ON  L46
L48 (          4)SEA FILE=REGISTRY ABB=ON  PLU=ON  L47 AND (C16H14N2O3S OR
                 C17H14O4S OR C16H9F5N2O3S OR C16H14N2O3S)/MF
L49 (         13)SEA FILE=REGISTRY ABB=ON  PLU=ON  L47 AND (C17H14F3N3O3S OR
                 C17H12F4N2O4S OR C17H16N2O4S OR C16H11CLF3N3O2S OR C17H12F2O4S
                 OR C16H13F2NO4S OR C17H14F3N3O2S OR C16H12F3N3O2S OR C17H14F3N3
                 O2S OR C17H12BRFO2S2 OR C13H18N2O5S OR C16H13F3N4O2S OR
                 C14H13N3O4S2)/MF
L50 (         17)SEA FILE=REGISTRY ABB=ON  PLU=ON  L48 OR L49
L51 (         40)SEA FILE=REGISTRY ABB=ON  PLU=ON  (123653-11-2/CRN OR 162011-90
                 -7/CRN OR 169590-41-4/CRN OR 170569-86-5/CRN OR 177660-77-4/CRN
                  OR 177660-80-9/CRN OR 177660-92-3/CRN OR 181695-72-7/CRN OR
                 185344-51-8/CRN OR 185344-55-2/CRN OR 195061-34-8/CRN OR
                 195065-56-6/CRN OR 195065-57-7/CRN OR 71125-38-7/CRN OR
                 80937-31-1/CRN OR 88149-94-4/CRN OR 93014-16-5/CRN)
L52 (         57)SEA FILE=REGISTRY ABB=ON  PLU=ON  L50 OR L51
L53 (         32)SEA FILE=REGISTRY ABB=ON  PLU=ON  L47 AND MAN/CI
L54 (         30)SEA FILE=REGISTRY ABB=ON  PLU=ON  L53 NOT (39391-18-9 OR
                 80619-02-9)/RN
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L55 (      1373)SEA FILE=REGISTRY ABB=ON  PLU=ON  CYCLOSPORIN/BI
L56 (      1403)SEA FILE=REGISTRY ABB=ON  PLU=ON  L54 OR L55
L57 (         2)SEA FILE=REGISTRY ABB=ON  PLU=ON  (39391-18-9 OR 80619-02-9)/RN

L58 (       120)SEA FILE=REGISTRY ABB=ON  PLU=ON  L47 NOT (L57 OR L56 OR L52)
L59 (      6040)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L58
L60 (      1841)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L52
L61 (     14626)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L56
L62 (        23)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L59 AND L60 AND L61
L63 (        57)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L60 AND L61
L64 (        34)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L63 NOT L62
L65           3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L64 AND ?LIPOXYGEN?
L66 (         1)SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2002-098644/AP,PRN
L67             SEL  PLU=ON  L66 1- RN :     169 TERMS
L68 (       169)SEA FILE=REGISTRY ABB=ON  PLU=ON  L67
L69 (         4)SEA FILE=REGISTRY ABB=ON  PLU=ON  L68 AND (C16H14N2O3S OR
                  C17H14O4S OR C16H9F5N2O3S OR C16H14N2O3S)/MF
L70 (        13)SEA FILE=REGISTRY ABB=ON  PLU=ON  L68 AND (C17H14F3N3O3S OR
                  C17H12F4N2O4S OR C17H16N2O4S OR C16H11CLF3N3O2S OR C17H12F2O4S
                  OR C16H13F2NO4S OR C17H14F3N3O2S OR C16H12F3N3O2S OR C17H14F3N3
                  O2S OR C17H12BRFO2S2 OR C13H18N2O5S OR C16H13F3N4O2S OR
                  C14H13N3O4S2)/MF
L71 (        17)SEA FILE=REGISTRY ABB=ON  PLU=ON  L69 OR L70
L72 (        40)SEA FILE=REGISTRY ABB=ON  PLU=ON  (123653-11-2/CRN OR 162011-90
                  -7/CRN OR 169590-41-4/CRN OR 170569-86-5/CRN OR 177660-77-4/CRN
                   OR 177660-80-9/CRN OR 177660-92-3/CRN OR 181695-72-7/CRN OR
                  185344-51-8/CRN OR 185344-55-2/CRN OR 195061-34-8/CRN OR
                  195065-56-6/CRN OR 195065-57-7/CRN OR 71125-38-7/CRN OR
                  80937-31-1/CRN OR 88149-94-4/CRN OR 93014-16-5/CRN)
L73 (        57)SEA FILE=REGISTRY ABB=ON  PLU=ON  L71 OR L72
L74 (        32)SEA FILE=REGISTRY ABB=ON  PLU=ON  L68 AND MAN/CI
L75 (        30)SEA FILE=REGISTRY ABB=ON  PLU=ON  L74 NOT (39391-18-9 OR
                  80619-02-9)/RN
L76 (      1373)SEA FILE=REGISTRY ABB=ON  PLU=ON  CYCLOSPORIN/BI
L77 (      1403)SEA FILE=REGISTRY ABB=ON  PLU=ON  L75 OR L76
L78 (         2)SEA FILE=REGISTRY ABB=ON  PLU=ON  (39391-18-9 OR 80619-02-9)/RN

L79 (       120)SEA FILE=REGISTRY ABB=ON  PLU=ON  L68 NOT (L78 OR L77 OR L73)
L80 (      6040)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L79
L81 (      1841)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L73
L82 (     14626)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L77
L83 (        23)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L80 AND L81 AND L82
L84 (        57)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L81 AND L82
L85 (        34)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L84 NOT L83
L86 (         3)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L85 AND ?LIPOXYGEN?
L87 (      9357)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (?LIPOXYGEN? (L) (?INHIBIT?
                  OR ?BLOCK? OR ?RUPT? OR ?DISABL?))
L88 (       201)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (?CYCLOXYGEN? (L) (?INHIBIT?
                  OR ?BLOCK? OR ?RUPT? OR ?DISABL?))
L89 (     15717)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (?CYCLOOXYGEN? (L) (?INHIBIT?
                  OR ?BLOCK? OR ?RUPT? OR ?DISABL?))
L90 (      7686)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (COX? (L) (?INHIBIT? OR
                  ?BLOCK? OR ?RUPT? OR ?DISABL?))
L91 (      9729)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (LIPOX? (L) (?INHIBIT? OR
                  ?BLOCK? OR ?RUPT? OR ?DISABL?))
L92 (      9731)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L87 OR L91
L93 (     18652)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L88 OR L89 OR L90)
L94 (     19593)SEA FILE=HCAPLUS ABB=ON  PLU=ON  ?CYCLOSPORIN?
L95 (        35)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L92 AND L93 AND L94
L96 (        28)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L95 NOT (L83 OR L86)
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L97 (   5876804) SEA FILE=HCAPLUS ABB=ON  PLU=ON  (?COMBIN? OR ?COMPOS? OR MIX?
                 OR ?MIXT? OR ?COMPN? OR ?COMBN?)
L98           12 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L96 AND L97
L99           16 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L39 OR L65 OR L98
L100           9 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L99 AND (AY<1997 OR PY<1997
                 OR PRY<1997)


=> d que 143
L1             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  39391-18-9/RN
L2             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  80619-02-9/RN
L3               SEL  PLU=ON  L1 1- CHEM :      36 TERMS
L4         22401 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3
L6         12138 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 (5A) (?INHIBIT? OR ?RUPT?
                 OR ?BLOCK? OR ?DISABL? OR ?STOP?)
L7               SEL  PLU=ON  L2 1- CHEM :      10 TERMS
L8          4694 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7
L9          3004 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 (5A) (?INHIBIT? OR ?RUPT?
                 OR ?BLOCK? OR ?DISABL? OR ?STOP?)
L10         6670 SEA FILE=HCAPLUS ABB=ON  PLU=ON  IMMUNOMODULATORS/CT
L11        16528 SEA FILE=HCAPLUS ABB=ON  PLU=ON  IMMUNOSUPPRESSANTS/CT
L12         8836 SEA FILE=HCAPLUS ABB=ON  PLU=ON  CYTOTOXIC AGENTS/CT
L13         4356 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (PROLIFERAT? (L) INHIB?)/CW
L14            0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANTIPROLIFERAT?/CW
L15        58930 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANTI-INFLAMMATORY AGENTS+PFT,N
                 T/CT
L16        32725 SEA FILE=HCAPLUS ABB=ON  PLU=ON  INFLAMMATION/CT
L17          377 SEA FILE=HCAPLUS ABB=ON  PLU=ON  TRANSPLANT AND TRANSPLANTATION
                 /CT
L18        53343 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (LEUKOCYT? OR LEUCOCYT?)/CW
L19            0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (ANTILEUKOCYT? OR ANTILEUCOCYT
                 ?)/CW
L20        19595 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ?CYCLOSPORIN?
L21       177028 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L10 OR L11 OR L12 OR L13 OR
                 L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20)
L23          410 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6 AND L9 AND L21
L40           24 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L23 AND REVIEW/DT
L42           18 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L40 AND (MIX? OR ?MIXT? OR
                 ?COMBIN? OR ?COMPRIS? OR ?COMPOS? OR COMB OR COMPN OR DUAL OR
                 ?SYNERG? OR BLEND)
L43           18 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L42 AND (L10 OR L11 OR L12 OR
                 L15 OR L20)


=> d l199 ibib abs hitind fhitstr hitrn
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y


L199 ANSWER 1 OF 23  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2003:991488  HCAPLUS
DOCUMENT NUMBER:          140:27834
TITLE:                    Preparation of pyridazinyloximes as phosphodiesterase
                          IV inhibitors.
INVENTOR(S):              Eggenweiler, Hans-Michael; Beier, Norbert; Schelling,
                          Pierre; Wolf, Michael
PATENT ASSIGNEE(S):       Merck Patent G.m.b.H., Germany
SOURCE:                   PCT Int. Appl., 137 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
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LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

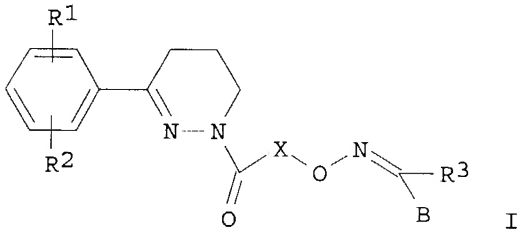
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003104205	A1	20031218	WO 2003-EP5173	20030516

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10225574	A1	20031218	DE 2002-10225574	20020610

PRIORITY APPLN. INFO.: DE 2002-10225574 A 20020610
OTHER SOURCE(S): MARPAT 140:27834
GI



I

AB Title compds. [I; R1, R2 = H, OH, OR8, SR8, SOR8, SO2R8, halo; R1R2 = OCH2O, OCH2CH2O; R3 = H, AR7, COAR7, CO2AR7, CONH2, NH2, etc.; R7 = H, CO2H, NH2, OH, etc.; R8 = (substituted) alkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, etc.; A = null, (O, S, SO, SO2, imino-interrupted) alkylene, alkenylene, cycloalkylene; B = (substituted) aryl, heteroaryl; X = (O, S, SO, SO2, imino-interrupted) alkylene], were prepared as phosphodiesterase IV inhibitors for treating osteoporosis, tumors, cachexia, atherosclerosis, rheumatoid arthritis, multiple sclerosis, diabetes mellitus, inflammatory processes, allergies, asthma, autoimmune diseases, myocardial diseases and AIDS (no data). Thus, 3-(3-ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazine was treated sequentially with chloroacetyl chloride, N-hydroxyphthalimide, ethanolamine, and 4-methoxybenzaldehyde to give 4-methoxybenzaldehyde O-[2-[3-(3-ethoxy-4-methoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]-2-oxoethyl]oxime.

IC ICM C07D237-04
ICS C07D401-12; A61K031-50; A61P037-00

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

IT 50-24-8, Prednisolone 53-03-2, Prednisone 57-22-7, Vincristine 57-66-9, Probenecid 57-96-5, Sulfinpyrazone 58-55-9, Theophylline, biological studies 59-05-2, Methotrexate 59-42-7, Phenylephrine 64-86-8, Colchicine 90-82-4, Pseudoephedrine 101-40-6, Propylhexedrine 113-92-8, Chlorpheniramine maleate 124-94-7D, Triamcinolone, acetonide derivative 315-30-0, Allopurinol 317-34-0, Aminophylline 404-86-4,

Capsaicin 446-86-6, Azathioprine 522-48-5, Tetrahydrozoline hydrochloride 550-99-2, Naphazoline hydrochloride 586-06-1, Metaproterenol 865-21-4, Vinblastine 1218-35-5, Xylometazoline hydrochloride 2315-02-8, Oxymetazoline hydrochloride 3198-07-0 3385-03-3, Flunisolide 3562-84-3, Benzbromarone 7440-57-5D, Gold, aurothio derivs. 7683-59-2, Isoproterenol 14838-15-4, Phenylpropanolamine 15826-37-6, Sodium cromoglycate 18559-94-9, Albuterol 22254-24-6, Ipratropium bromide 23031-25-6, Terbutalin 28797-61-7, Pirenzepin 30286-75-0, Oxitropium bromide 30392-40-6, Bitolterol 38677-81-5, Pirbuterol 51333-22-3, Budesonide 58581-89-8, Azelastine **59865-13-3**, Cyclosporin 68844-77-9, Astemizole 73573-87-2, Formoterol 75706-12-6, Leflunomide 79794-75-5, Loratadine 80880-90-6, Telenzepine 83799-24-0, Fexofenadine 83869-56-1, GM-CSF 83881-51-0, Cetirizine 89365-50-4, Salmeterol **93211-49-5**, L-651392 96566-25-5, Ablukast 100643-71-8, Desloratadine 103177-37-3, Pranlukast **103475-41-8**, Tepoxalin 106096-93-9, Basic fibroblast growth factor 107753-78-6, Zafirlukast **111406-87-2**, Zileuton **118414-82-7**, Mk-886 120128-20-3, RG-12525 120443-16-5, Verlukast 126544-47-6, Ciclesonide **128253-31-6**, Bay x 1005 136310-93-5, Tiotropium bromide **140841-32-3**, Zd-2138 **141579-54-6**, Fenleuton **141579-87-5**, Abbott 79175 143538-27-6, Bay x 7195 **147030-01-1**, Mk-591 147398-01-4, CGS-25019c 147432-77-7, Ontazolast 151581-24-7, Iralukast **154355-76-7**, Abbott 85761 **158930-07-5**, L-739010 158966-92-8, Montelukast **162011-90-7**, Rofecoxib 162750-10-9, Sb-210661 168154-07-2, L-746530 170277-31-3, Infliximab 171964-73-1, ZD-0892 174636-32-9, Talnetant 185243-69-0, Etanercept 204974-93-6, BIIL 260 257892-34-5, D-4418 331731-18-1, D2E7 346735-24-8, BIIL 284 350610-64-9, NKP-608c 446023-33-2, UT-77 634206-58-9D, hydrazone derivative

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (coadministration; preparation of pyridazinyloximes as phosphodiesterase IV inhibitors)

IT **59865-13-3**, Cyclosporin

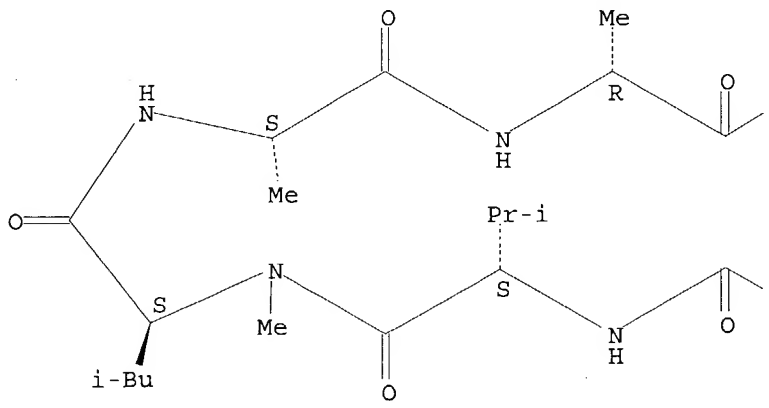
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (coadministration; preparation of pyridazinyloximes as phosphodiesterase IV inhibitors)

RN 59865-13-3 HCAPLUS

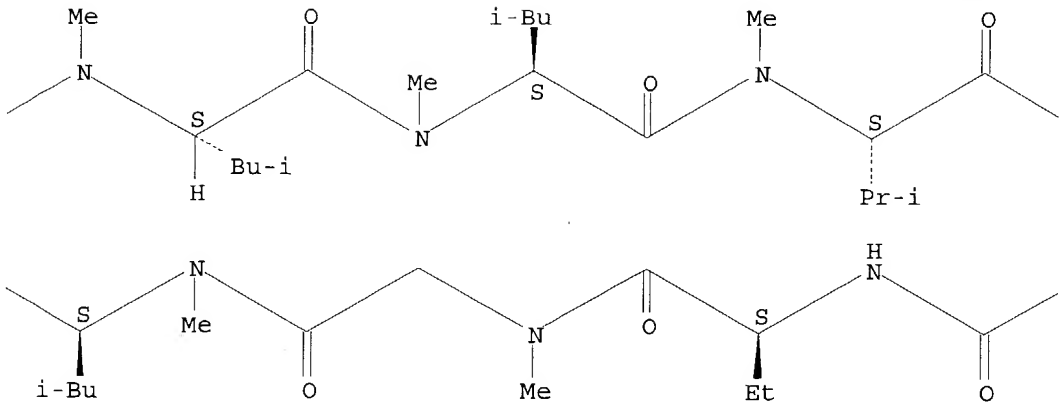
CN Cyclosporin A (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

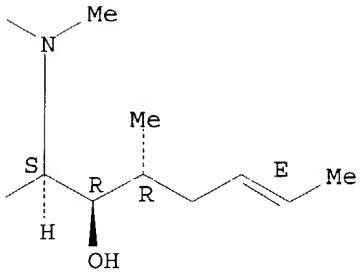
PAGE 1-A



PAGE 1-B



PAGE 1-C



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103475-41-8, Tepoxalin **111406-87-2**, Zileuton
118414-82-7, Mk-886 **128253-31-6**, Bay x 1005
140841-32-3, Zd-2138 **141579-54-6**, Fenleuton
141579-87-5, Abbott 79175 **147030-01-1**, Mk-591
154355-76-7, Abbott 85761 **158930-07-5**, L-739010
162011-90-7, Rofecoxib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coadministration; preparation of pyridazinyloximes as phosphodiesterase IV inhibitors)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l199 ibib abs hitind fhitstr hitrn 2-
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y

YOU HAVE REQUESTED DATA FROM 22 ANSWERS - CONTINUE? Y/(N):y

L199 ANSWER 2 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:991487 HCAPLUS
DOCUMENT NUMBER: 140:42462
TITLE: Synthesis of tyrosinyl or alaninyl pyridazine derivatives for use as phosphodiesterase IV inhibitors for the treatment of allergic, autoimmune and inflammatory diseases
INVENTOR(S): Eggenweiler, Hans-Michael; Wolf, Michael
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 129 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003104204	A1	20031218	WO 2003-EP4930	20030512
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10224888	A1	20031224	DE 2002-10224888	20020605

PRIORITY APPLN. INFO.: DE 2002-10224888 A 20020605
OTHER SOURCE(S): MARPAT 140:42462
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Synthesis of title compds., e.g. (I,III), which act as phosphodiesterase IV inhibitors and can be used for treating osteoporosis, tumors, cachexia, atherosclerosis, rheumatoid arthritis, multiple sclerosis, diabetes mellitus, inflammatory processes, allergies, asthma, autoimmune diseases, myocardial diseases, and AIDS (no data), was given. Thus, Z-L-Tyr(tBu)-OSu was reacted with (II), the tBu protecting group cleaved, and the resulting intermediate reacted with Cl-(CH2)2NMe2.HCl to give an intermediate which was Tyr-N-deprotected to give I. Similarly, Boc-β-(3-pyridyl)-D-Ala-OH led to III. In vitro tests for effectiveness were described without results, and formulations for various forms of administration were given.

IC ICM C07D237-04
ICS C07D401-12; C07D401-06

CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 7, 25, 27, 28, 63

IT **141579-87-5**, Abbott 79175
RL: MSC (Miscellaneous)
(Abbott 79175; compds. containing tyrosinyl or alaninyl pyridazine derivs. and for use as phosphodiesterase IV inhibitors for the treatment of

diseases)

IT 50-24-8, Prednisolone 53-03-2, Prednisone 57-22-7, Vincristin 57-66-9, Probenecid 57-96-5, Sulfinpyrazone 58-55-9, Theophylline, miscellaneous 59-05-2, Methotrexate 59-42-7, Phenylephrine 76-25-5, Triamcinolone acetonide 90-82-4, Pseudoephedrine 101-40-6, Propylhexedrine 315-30-0, Allopurinol 317-34-0, Aminophylline 404-86-4, Capsaicine 446-86-6, Azathioprine 522-48-5, Tetrahydrozoline hydrochloride 550-99-2, Naphazoline hydrochloride 586-06-1, Metaproterenol 865-21-4, Vinblastin 1218-35-5, Xylometazoline hydrochloride 2315-02-8, Oxymetazoline hydrochloride 3198-07-0 3385-03-3, Flunisolide 3562-84-3, Benzbromaron 5534-09-8, Beclomethasone dipropionate 7683-59-2, Isoproterenol 9004-08-4, Cathepsin 14838-15-4, Phenylpropanolamine 15826-37-6, Sodium cromoglycate 18559-94-9, Albuterol 22254-24-6, Ipratropium bromide 23031-25-6, Terbutaline 28797-61-7, Pirenzepine 30286-75-0, Oxitropium bromide 30392-40-6, Bitolterol 38677-81-5, Pirbuterol 51333-22-3, Budesonide 58581-89-8, Azelastine 68844-77-9, Astemizole 73573-87-2, Formoterol 75706-12-6, Leflunomide **79217-60-0**, Cyclosporin 79794-75-5, Loratadine 79955-99-0, Stromelysin-1 80474-14-2, Fluticasone propionate 80880-90-6, Telenzepine 83799-24-0, Fexofenadine 83869-56-1, Granulocyte macrophage colony stimulating factor 83881-51-0 83919-23-7, Mometasone furoate 89365-50-4, Salmeterol **93211-49-5**, 1651392 96566-25-5, Ablukast 100643-71-8, Desloratadine 103177-37-3, Pranlukast **103475-41-8**, Tepoxalin 106096-93-9 107753-78-6, Zafirlukast **111406-87-2**, Zileuton **118414-82-7**, Mk886 120128-20-3, Rg12525 120443-16-5, Verlukast 126544-47-6, Ciclesonide **128253-31-6**, Bay x1005 136310-93-5, Tiotropium bromide 140610-48-6, Stromelysin-2 **140841-32-3**, Zd2138 **141579-54-6**, Fenleuton 143538-27-6, Bay x7195 145267-01-2, Stromelysin-3 **147030-01-1**, Mk591 147398-01-4, Cgs25019c 147432-77-7, Ontazolast 151581-24-7, Iralukast **154355-76-7**, Abt761 **158930-07-5**, l739010 158966-92-8, Montelukast **162011-90-7**, Rofecoxib 162750-10-9, Sb210661 168154-07-2, l746530 170277-31-3, Infliximab 171964-73-1 174636-32-9, Talnetant 185243-69-0, Etanercept 204974-93-6, Biil 284/260 257892-34-5, d4418 331731-18-1, d2e7 350610-64-9, Nkp608c 446023-33-2, UT 77

RL: MSC (Miscellaneous)

(compds. containing tyrosinyl or alaninyl pyridazine derivs. and for use as phosphodiesterase IV inhibitors for the treatment of diseases)

IT **141579-87-5**, Abbott 79175

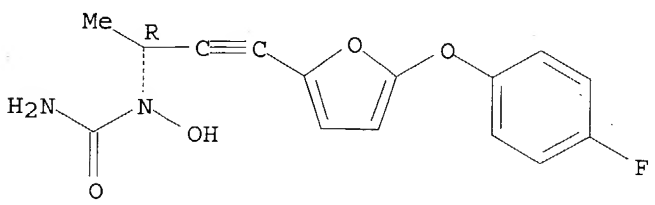
RL: MSC (Miscellaneous)

(Abbott 79175; compds. containing tyrosinyl or alaninyl pyridazine derivs. and for use as phosphodiesterase IV inhibitors for the treatment of diseases)

RN 141579-87-5 HCAPLUS

CN Urea, N-[(1R)-3-[5-(4-fluorophenoxy)-2-furanyl]-1-methyl-2-propynyl]-N-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT **141579-87-5**, Abbott 79175
RL: MSC (Miscellaneous)
(Abbott 79175; compds. containing tyrosinyl or alaninyl pyridazine derivs. and for use as phosphodiesterase IV inhibitors for the treatment of diseases)
IT **79217-60-0**, Cyclosporin **93211-49-5**, 1651392
103475-41-8, Tepoxalin **111406-87-2**, Zileuton
118414-82-7, Mk886 **128253-31-6**, Bay x1005
140841-32-3, Zd2138 **141579-54-6**, Fenleuton
147030-01-1, Mk591 **154355-76-7**, Abt761
158930-07-5, 1739010 **162011-90-7**, Rofecoxib
RL: MSC (Miscellaneous)
(compds. containing tyrosinyl or alaninyl pyridazine derivs. and for use as phosphodiesterase IV inhibitors for the treatment of diseases)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L199 ANSWER 3 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:971836 HCAPLUS
DOCUMENT NUMBER: 140:23256
TITLE: Combination therapy for treatment of amyotrophic lateral sclerosis (ALS) with cyclooxygenase-2 (COX 2) inhibitor(s) and a second drug
INVENTOR(S): Isakson, Peter C.
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: PCT Int. Appl., 358 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003101380	A2	20031211	WO 2003-US14547	20030528
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004063751	A1	20040401	US 2003-444071	20030523

PRIORITY APPLN. INFO.: US 2002-384104P P 20020531
US 2003-444071 A 20030523

OTHER SOURCE(S): MARPAT 140:23256
AB A method of treating, preventing, or inhibiting ALS, in a subject in need of such treatment, inhibition or prevention. The method comprises administering to a subject one or more cyclooxygenase-2 selective inhibitor(s) or isomer(s) or pharmaceutically acceptable salt(s), ester(s), or prodrug(s) thereof, in combination with one or more second drugs, wherein the amount of the cyclooxygenase-2 selective inhibitor(s) or isomer(s) or pharmaceutically acceptable salt(s), ester(s), or prodrug(s) thereof in combination with the amount of second drug(s) constitutes an ALS treatment, inhibition or prevention effective amount
IC ICM A61K

CC 1-11 (Pharmacology)
Section cross-reference(s): 2, 15, 63

IT 50-18-0, Cyclophosphamide 50-48-6 50-78-2, Aspirin 50-81-7, Vitamin c, biological studies 51-34-3, SCopolamine 53-39-4, Oxandrolone 53-43-0, Dhea 54-11-5, Nicotine 54-96-6, 3,4-Diaminopyridine 57-00-1, Creatine 57-27-2, Morphine, biological studies 57-42-1, Pethidine 60-54-8, Tetracycline 61-90-5, Leucine, biological studies 70-18-8, Glutathione, biological studies 71-30-7, Cytosine 72-18-4, Valine, biological studies 72-19-5, Threonine, biological studies 73-32-5, Isoleucine, biological studies 76-42-6, Oxycodone 76-99-3, Methadone 77-10-1 89-25-8, Edaravone 90-69-7, Lobeline 93-14-1, Robitussin 103-90-2, Acetaminophen 120-29-6, Tropine 125-71-3, Dextromethorphan 144-11-6, Trihexyphenidyl 145-13-1, Pregnenolone 147-24-0, Benadryl 298-50-0, Propantheline 303-98-0, Co-enzyme q10 439-14-5, Diazepam 446-72-0, Genistein 446-86-6, Azathioprine 469-79-4, Ketobemidone 494-52-0, Anabasine 500-38-9, Nordihydroguaiaretic acid 564-25-0, Doxycycline 577-11-7, Colace 596-51-0, Glycopyrrolate 616-91-1, Acetylcysteine 846-49-1, Lorazepam 1077-28-7, DL-.α.-Lipoic acid 1134-47-0, Lioresal 1622-61-3, Klonopin 1744-22-5, Riluzole 1972-08-3, Dronabinol 2259-96-3, Cyclothiazide) 2323-36-6, Deprenyl 2379-57-9, DNQX 4205-90-7, Clonidine 6740-88-1, Ketamine 7235-40-7, Beta carotene 7261-97-4, Dantrolene 7782-49-2, Selenium, biological studies 9001-05-2, Catalase 9013-66-5, Glutathione peroxidase 9054-89-1, Superoxide dismutase 9061-61-4, Ngf 10118-90-8, Minocycline 10540-29-1, Tamoxifen 11006-70-5, Olivomycin 11096-26-7, Erythropoietin 13422-55-4, Methylcobalamin 15687-27-1, Ibuprofen 18378-89-7, Mithramycin 19771-63-2, Procysteine 19982-08-2, Memantine 20830-81-3, Daunomycin 22503-72-6, IDRA 21) 23052-80-4 23052-81-5 27203-92-5, Tramadol 29529-99-5, Pc 10 36505-84-7, Buspirone 51803-78-2, Nimesulide 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine **59865-13-3**, Cyclosporine 60142-96-3, Gabapentin 64461-82-1, Zanaflex 66357-35-5, Ranitidine 66537-55-1, Mk-771 67684-64-4 **71125-38-7**, Meloxicam 73384-59-5, Ceftriaxone 74913-06-7, Chromomycin 76326-31-3 76820-40-1, Rx-77368 76824-35-6, Famotidine 77086-21-6, Dizocilpine 78794-60-2 79617-96-2, Sertraline **80937-31-1**, Flosulide 84057-84-1, Lamotrigine 85148-82-9 90494-79-4, Xaliproden hydrochloride **93014-16-5** 93384-43-1, Botulinum toxin type a 97240-79-4, Topiramate 100828-16-8 102518-79-6, Huperzine a 102771-26-6, GYKI 52466 103300-74-9, Ta-0910 103548-82-9, Huperzine b 104325-83-9, l-655238 110347-85-8, Selfotel **111406-87-2**, Zileuton 115066-14-3, CNQX 116049-53-7, CGP 40116 118876-58-7 119431-25-3, Eliprodil **123653-11-2**, NS-398 123663-49-0, t-614 124937-52-6, Detrol 125978-95-2, Nitric oxide synthase 126114-66-7, FR 115427 **127245-22-1**, Bf-389 127464-60-2, Vascular endothelial growth factor 127910-31-0, CGP 37849 127910-32-1, CGP 39551 **128253-31-6**, Bay-x-1005 130939-66-1, Neurotrophin-3 134052-73-6, (S)-4-Carboxyphenylglycine 135354-02-8, Xaliproden 137159-92-3, Aptiganel 139226-28-1, Darbufelone 140111-52-0, Epibatidine 142935-03-3, t-588 143375-33-1, Neurotrophin-4/5 143809-38-5 143809-39-6 144301-37-1, NPC 17742 145464-27-3, Immune globulin intravenous pentetate 146669-29-6 147245-92-9, Copaxone 147750-87-6, NS 257 147782-19-2, DCGIV 148152-77-6, Jtp-2942 150010-68-7, LY 215490 150378-17-9, Indinavir **156897-06-2**, Ml-3000 157381-42-5 158205-05-1, L-745337 158959-32-1 158959-33-2 158959-34-3 158959-35-4 158959-37-6 158959-42-3 158959-43-4 158959-46-7 158959-47-8 158959-56-9 159075-60-2, Emfilermin 159429-69-3 159429-70-6 161832-65-1, LY-300164 **162011-90-7**, Rofecoxib 162054-19-5 163303-19-3 163303-25-1 163303-29-5 163303-38-6 163303-55-7 165251-89-8 165328-42-7 165328-49-4

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169902-71-0 169902-74-3 169902-75-4 169951-23-9 169951-24-0
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177560-61-1 177660-54-7 177660-55-8 177660-56-9 177660-67-2
177660-72-9 177660-73-0 177660-76-3 **177660-77-4**
177660-80-9 177660-81-0 177660-85-4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy for amyotrophic lateral sclerosis treatment of with COX-2 inhibitor and second drug)

IT 177660-89-8 **177660-92-3** 177660-94-5 177661-00-6
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177754-42-6 179382-91-3 179464-49-4, Sc-55858 180132-69-8, Cardiotrophin-1 180200-68-4, JTE-522 181627-94-1 181627-96-3
181627-98-5 181628-00-2 **181695-72-7**, Valdecoxib 181695-81-8
181695-85-2 181696-18-4 181696-33-3 181809-58-5 181809-60-9
181809-63-2 183610-65-3 183734-91-0, RPR-119990 **185344-55-2**
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197438-48-5, BMS-347070 197980-93-1, Pigment epithelium derived factor
198470-84-7, Parecoxib 198470-85-8 202409-33-4, Etoricoxib
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(combination therapy for amyotrophic lateral sclerosis treatment of with COX-2 inhibitor and second drug)

IT **59865-13-3**, Cyclosporine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(combination therapy for amyotrophic lateral sclerosis treatment of with COX-2 inhibitor and second drug)

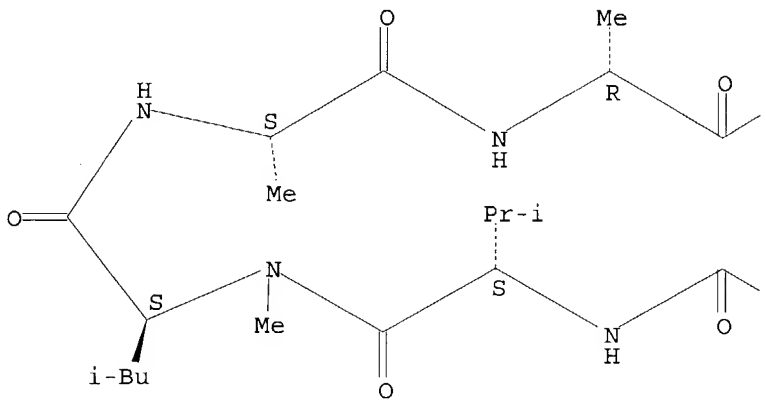
RN 59865-13-3 HCAPLUS

CN Cyclosporin A (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as shown.

PAGE 1-A



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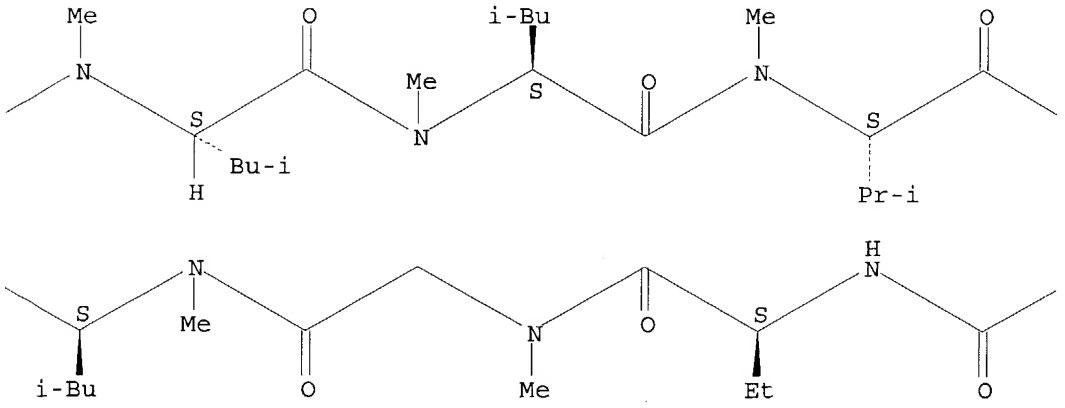

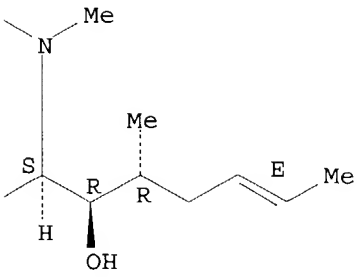

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(combination therapy for amyotrophic lateral sclerosis treatment of with COX-2 inhibitor and second drug)

L199 ANSWER 4 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:376641 HCAPLUS
DOCUMENT NUMBER: 138:385438
TITLE: Preparation of pyridazinylmethanoylphenylhydrazonomalonitriles as phosphodiesterase IV inhibitors.
INVENTOR(S): Eggenweiler, Hans-Michael; Wolf, Michael; Beier, Norbert; Schelling, Pierre; Ehring, Thomas
PATENT ASSIGNEE(S): Merck Patent Gmbh, Germany
SOURCE: PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003039548	A1	20030515	WO 2002-EP11351	20021010

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: EP 2001-125455 A 20011105
OTHER SOURCE(S): MARPAT 138:385438

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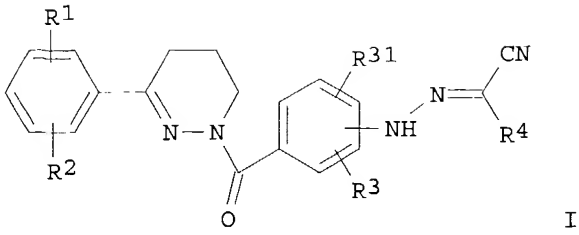


I

AB Title compds. [I; R1, R2 = H, OH, OR5, SR5, SOR5, SO2R5, X; R1R2 = OCH2O, OCH2CH2O; R3, R31 = H, R5, OH, OR5, NH2, NHR5, NHCOR5, X, CO2H, CO2R5, CONH2, etc.; R4 = cyano, tetrazolyl; R5 = (fluoro-substituted) A, cycloalkyl, (CH2)nAr; A = (fluoro- and/or chloro-substituted) alkyl, alkenyl; Ar = Ph; n = 0-2; X = F, Cl, Br, iodo], were prepared Thus, [3-(3,4-diethoxyphenyl)-5,6-dihydro-4H-pyridazine-1-yl]-(3-aminophenyl)methanone (preparation given) was stirred with NaNO2 in aqueous HCl for 1 h at -2° to 0°; malononitrile in H2O was added followed by stirring for 2 h to give a residue which was treated with KOH in MeOH to give 2-[[3-[1-[3-(3,4-diethoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]methanoyl]phenyl]hydrazono]malononitrile K salt. I were said to give a marked reduction of T cell proliferation. I are claimed for treatment of osteoporosis, tumors, cachexia, atherosclerosis, rheumatoid arthritis, multiple sclerosis, diabetes mellitus, inflammatory processes, allergies, asthma, autoimmune diseases, myocardial diseases, AIDS, etc.

IC ICM A61K031-50
ICS C07D237-04

CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

IT 50-24-8, Prednisolone 53-03-2, Prednisone 57-22-7, Vincristine 57-66-9, Probenecid 57-96-5, Sulfinpyrazone 58-55-9, Theophylline, biological studies 59-05-2, Methotrexate 59-42-7, Phenylephrine 76-25-5, Triamcinolone acetonide 90-82-4, Pseudoephedrine 101-40-6, Propylhexedrine 113-92-8, Chlorpheniramine 315-30-0, Allopurinol 317-34-0, Aminophylline 404-86-4, Capsaicin 446-86-6, Azathioprine 522-48-5, Tetrahydrozoline hydrochloride 550-99-2, Naphazoline hydrochloride 586-06-1, Metaproterenol 865-21-4, Vinblastine 1218-35-5, Xylometazoline hydrochloride 1397-89-3, Amphotericin b 2315-02-8, Oxymetazoline hydrochloride 3198-07-0 3385-03-3, Flunisolide 3562-84-3, Benzbromarone 5534-09-8, Beclomethasone dipropionate 7440-57-5D, Gold, aurothio compds. 7683-59-2, Isoproterenol 14838-15-4, Phenylpropanolamine 15826-37-6, Sodium cromoglycate 18559-94-9, Albuterol 22254-24-6, Ipratropium bromide 22916-47-8, Miconazole 23031-25-6, Terbutaline 23593-75-1, Clotrimazole 27220-47-9, Econazole 28797-61-7, Pirenzepine 30286-75-0, Oxitropium bromide 30392-40-6, Bitolterol 38677-81-5, Pirbuterol 51333-22-3, Budesonide 58581-89-8, Azelastine **59865-13-3**, Cyclosporine 65277-42-1, Ketoconazole 67763-96-6, IGF-1 68844-77-9, Astemizole 73573-87-2, Formoterol 75706-12-6, Leflunomide 79794-75-5, Loratidine 80474-14-2, Fluticasone propionate 80880-90-6, Telenzepine 83799-24-0, Fexofenadine 83869-56-1, GM-CSF 83881-51-0, Cetirizine 83919-23-7, Mometasone furoate 84625-61-6, Itraconazole 86386-73-4, Fluconazole 89365-50-4, Salmeterol **93211-49-5**, L-651392 96566-25-5, Ablukast 100643-71-8, Desloratadine 103177-37-3, Pranlukast **103475-41-8**, Tepoxalin

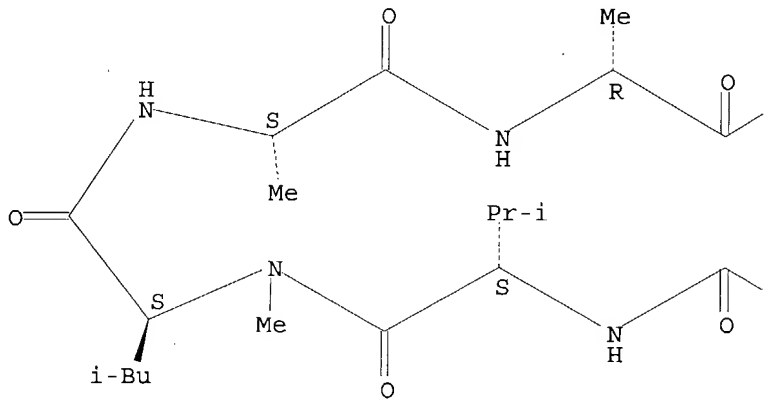
106096-93-9, Basic fibroblast growth factor 107753-78-6, Zafirlukast **111406-87-2**, Zileuton **118414-82-7**, Mk-886 120128-20-3, RG-12525 120443-16-5, Verlukast 126544-47-6, Ciclesonide **128253-31-6**, BAY-X 1005 128312-51-6, Ro 24-5913 136310-93-5, Tiotropium bromide **140841-32-3**, Zd-2138 **141579-54-6**, Fenleuton **141579-87-5**, Abbott 79175 143538-27-6, BAY-X 7195 **147030-01-1**, Mk-591 147398-01-4, CGS-25019c 147432-77-7, Ontazolast 151581-24-7, Iralukast **154355-76-7**, Abt-761 **158930-07-5**, L-739010 158966-92-8, Montelukast **162011-90-7**, Rofecoxib 162750-10-9, Sb-210661 168154-07-2, L-746530 170277-31-3, Infliximab 171964-73-1, Zd0892 174636-32-9, Talnetant 185243-69-0, Etanercept 202415-99-4, IPL 576092 204974-93-6, BIIL 284/260 257892-34-5, D-4418 331731-18-1, D 2E7 350610-64-9, NKP 608C 446023-33-2, UT-77
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coadministration; preparation of pyridazinylmethanoylphenylhydrazonomalonitriles as phosphodiesterase IV inhibitors)

IT **59865-13-3**, Cyclosporine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coadministration; preparation of pyridazinylmethanoylphenylhydrazonomalonitriles as phosphodiesterase IV inhibitors)

RN 59865-13-3 HCAPLUS
CN Cyclosporin A (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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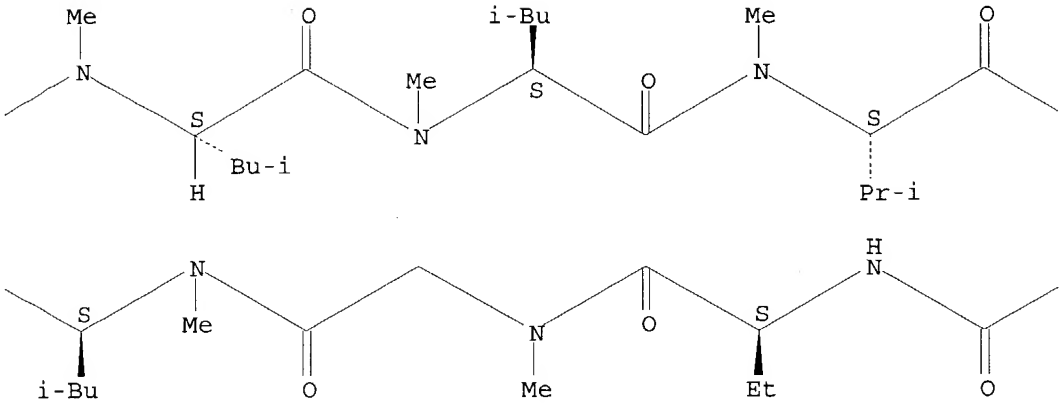

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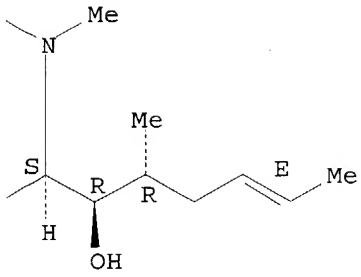

IT **59865-13-3**, Cyclosporine **93211-49-5**, L-651392
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154355-76-7, Abt-761 **158930-07-5**, L-739010
162011-90-7, Rofecoxib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coadministration; preparation of pyridazinylmethanoylphenylhydrazonomalonit
riles as phosphodiesterase IV inhibitors)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L199 ANSWER 5 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:356269 HCAPLUS
DOCUMENT NUMBER: 138:348761
TITLE: Type 4 phosphodiesterase inhibitors and therapeutic uses thereof
INVENTOR(S): Eggenweiler, Hans-Michael; Wolf, Michael
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 122 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003037349	A1	20030508	WO 2002-EP9596	20020828

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: EP 2001-125394 A 20011031
OTHER SOURCE(S): MARPAT 138:348761

AB The invention discloses the use of type 4 phosphodiesterase inhibitors (PDE IV inhibitors) to treat diseases, as well as combinations of PDE IV inhibitors with other drugs.

IC ICM A61K031-54
ICS A61K031-495; A61K031-50; A61P011-06; A61P017-06; A61P029-00; A61P037-00

CC 1-12 (Pharmacology)

IT 57-22-7, Vincristine 57-66-9, Probenecid 57-96-5, Sulfinpyrazone 59-05-2, Methotrexate 64-86-8, Colchicine 315-30-0, Allopurinol 446-86-6, Azathioprine 865-21-4, Vinblastine 3562-84-3, Benzbromarone 9004-08-4, Cathepsin **59865-13-3**, Cyclosporine 75706-12-6, Leflunomide 106096-93-9, Basic fibroblast growth factor 170277-31-3, Infliximab 185243-69-0, Etanercept 331731-18-1, D2E7
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
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RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(phosphodiesterase IV inhibitors, therapeutic uses, and use with other
agents)

IT 50-24-8, Prednisolone 53-03-2, Prednisone 58-55-9, Theophylline,
biological studies 59-42-7, Phenylephrine 76-25-5, ,Triamcinolone
acetonide 90-82-4, Pseudoephedrine 101-40-6, Propylhexedrine
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1218-35-5, ,Xylometazoline hydrochloride 2315-02-8, ,Oxymetazoline
hydrochloride 3198-07-0 3385-03-3, Flunisolide 5534-09-8, ,
Beclomethasone dipropionate 7683-59-2, Isoproterenol 14838-15-4,
Phenylpropanolamine 15826-37-6, Sodium cromoglycate; 18559-94-9, ,

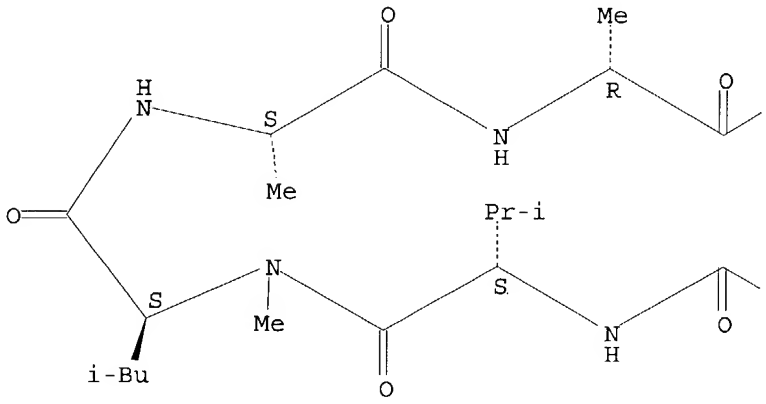
Albuterol 22254-24-6, Ipratropium bromide 23031-25-6, Terbutaline 28797-61-7, Pirenzepine 30286-75-0, Oxitropium bromide 30392-40-6, Bitolterol 38677-81-5, Pirbuterol 51333-22-3, Budesonide 73573-87-2, Formoterol 80474-14-2, ,Fluticasone propionate 80880-90-6, Telenzepine 83919-23-7, Mometasone furoate 89365-50-4, Salmeterol 126544-47-6, Ciclesonide 136310-93-5, ; Tiotropium bromide **162011-90-7**, Rofecoxib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sphosphodiesterase IV inhibitors, therapeutic uses, and use with other agents)

IT **59865-13-3**, Cyclosporine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(msphosphodiesterase IV inhibitors, therapeutic uses, and use with other agents)

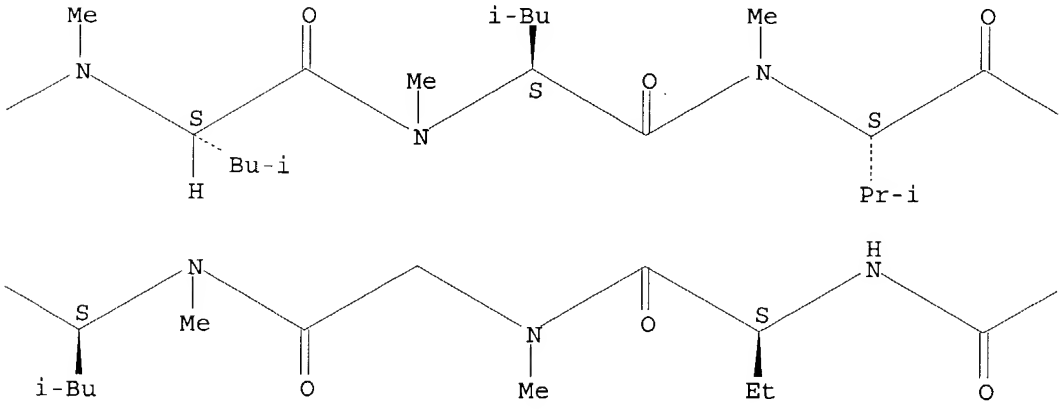
RN 59865-13-3 HCAPLUS
CN Cyclosporin A (9CI) (CA INDEX NAME)

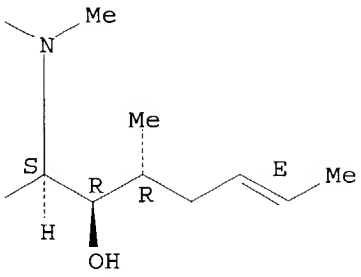
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B





IT **59865-13-3**, Cyclosporine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(msphosphodiesterase IV inhibitors, therapeutic uses, and use with other agents)
IT **93211-49-5**, L-651392 **103475-41-8**, Tepoxalin
111406-87-2, Zileuton **118414-82-7**, MK-886
128253-31-6, BAY x 1005 **140841-32-3**, ZD-2138
141579-54-6, Fenleuton **141579-87-5**, A 79175
147030-01-1, MK-591 **154355-76-7**, ; ABT-761
158930-07-5, L-739010
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphodiesterase IV inhibitors, therapeutic uses, and use with other agents)
IT **162011-90-7**, Rofecoxib
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sphosphodiesterase IV inhibitors, therapeutic uses, and use with other agents)
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L199 ANSWER 6 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:202410 HCAPLUS
DOCUMENT NUMBER: 138:226705
TITLE: Novel pharmaceuticals comprising drug conjugates with polypeptide carriers
INVENTOR(S): Picariello, Thomas
PATENT ASSIGNEE(S): New River Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 2059 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003020200	A2	20030313	WO 2001-US43117	20011116

WO 2003020200 A3 20030912
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
EP 1357928 A2 20031105 EP 2001-273387 20011116
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.:

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US 2000-248603P	P	20001116
US 2000-248604P	P	20001116
US 2000-248606P	P	20001116
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US 2001-248833P	P	20011116
US 2001-248848P	P	20011116
US 2001-248849P	P	20011116
WO 2001-US43117	W	20011116

AB A pharmaceutical composition comprising a polypeptide and an active agent attached to said polypeptide is disclosed.

IC ICM A61K

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 2, 15

IT 50-06-6D, Phenobarbital, polypeptide conjugates 50-35-1D, Thalidomide, polypeptide conjugates 50-81-7D, Vitamin c, polypeptide conjugates 51-21-8D, Fluorouracil, polypeptide conjugates 51-48-9D, Levothyroxine, polypeptide conjugates 52-01-7D, Spironolactone, polypeptide conjugates 52-24-4D, Thiotepa, polypeptide conjugates 52-53-9D, Verapamil, polypeptide conjugates 53-03-2D, Prednisone, polypeptide conjugates 55-63-0D, Nitroglycerin, polypeptide conjugates 57-27-2D, Morphine, polypeptide conjugates 57-41-0D, Phenytoin, polypeptide conjugates 57-63-6D, Ethinyl estradiol, polypeptide conjugates 58-55-9D, Theophylline, polypeptide conjugates 58-93-5D, Hydrochlorothiazide, polypeptide conjugates 60-54-8D, Tetracycline, polypeptide conjugates 60-87-7D, Promethazine, polypeptide conjugates 67-20-9D, Nitrofurantoin, polypeptide conjugates 68-19-9D, Vitamin b12, polypeptide conjugates 68-22-4D, Norethindrone, polypeptide conjugates 71-58-9D, Medroxyprogesterone acetate, polypeptide conjugates 72-69-5D, Nortriptyline, polypeptide conjugates 74-79-3D, Arginine, polypeptide conjugates 76-42-6D, Oxycodone, polypeptide conjugates 76-57-3D, Codeine, polypeptide conjugates 81-81-2D, Warfarin, polypeptide conjugates 83-43-2D, Methylprednisolone, polypeptide conjugates 84-02-6D, Prochlorperazine maleate, polypeptide conjugates 87-08-1D, Penicillin v, polypeptide conjugates 89-57-6D, Mesalamine, polypeptide conjugates 90-82-4D, Pseudoephedrine, polypeptide conjugates 99-66-1D, Valproic acid, polypeptide conjugates 103-90-2D, Acetaminophen, polypeptide conjugates 113-45-1D, Methylphenidate, polypeptide conjugates 114-07-8D, Erythromycin, polypeptide conjugates 125-33-7D, Primidone, polypeptide conjugates 128-13-2D, Ursodiol, polypeptide conjugates 396-01-0D, Triamterene, polypeptide conjugates 443-48-1D, Metronidazole, polypeptide conjugates 469-62-5D, Propoxyphene, polypeptide conjugates 525-66-6D, Propranolol, polypeptide conjugates 541-15-1D, Levocarnitine, polypeptide conjugates 554-13-2D, Lithium

carbonate, polypeptide conjugates 595-33-5D, Megestrol acetate, polypeptide conjugates 604-75-1D, Oxazepam, polypeptide conjugates 657-24-9D, Metformin, polypeptide conjugates 846-49-1D, Lorazepam, polypeptide conjugates 846-50-4D, Temazepam, polypeptide conjugates 1247-42-3D, Methylprednisone, polypeptide conjugates 1404-90-6D, Vancomycin, polypeptide conjugates 1508-65-2D, Oxybutynin chloride, polypeptide conjugates 1665-48-1D, Metaxalone, polypeptide conjugates 1744-22-5D, Riluzole, polypeptide conjugates 2078-54-8D, Propofol, polypeptide conjugates 2152-34-3D, Pemoline, polypeptide conjugates 3056-17-5D, Stavudine, polypeptide conjugates 3930-20-9D, Sotalol, polypeptide conjugates 4682-36-4D, Orphenadrine citrate, polypeptide conjugates 6493-05-6D, Pentoxifylline, polypeptide conjugates 6893-02-3D, TriIodothyronine, polypeptide conjugates 9002-69-1D, Relaxin, polypeptide conjugates 9004-10-8D, Insulin, polypeptide conjugates 9005-49-6D, Heparin, polypeptide conjugates 9014-42-0D, Thrombopoietin, polypeptide conjugates 9039-53-6D, Urokinase, polypeptide conjugates 10118-90-8D, Minocycline, polypeptide conjugates 10540-29-1D, Tamoxifen, polypeptide conjugates 11056-06-7D, Bleomycin, polypeptide conjugates 13392-28-4D, Rimantadine, polypeptide conjugates 14611-51-9D, Selegiline, polypeptide conjugates 17560-51-9D, Metolazone, polypeptide conjugates 19767-45-4D, Mesna, polypeptide conjugates 19794-93-5D, Trazodone, polypeptide conjugates 21256-18-8D, Oxaprozin, polypeptide conjugates 21829-25-4D, Nifedipine, polypeptide conjugates 22204-53-1D, Naproxen, polypeptide conjugates 23031-32-5D, Terbutaline sulfate, polypeptide conjugates 27203-92-5D, Tramadol, polypeptide conjugates 27314-97-2D, Tirapazamine, polypeptide conjugates 30516-87-1D, Zidovudine, polypeptide conjugates 31441-78-8D, Mercaptopurine, polypeptide conjugates 33069-62-4D, Paclitaxel, polypeptide conjugates 36791-04-5D, Ribavirin, polypeptide conjugates 37300-21-3D, Pentosan polysulfate, polypeptide conjugates 40391-99-9D, polypeptide conjugates 42200-33-9D, Nadolol, polypeptide conjugates 42924-53-8D, Nabumetone, polypeptide conjugates 49842-07-1D, Tobramycin sulfate, polypeptide conjugates 50700-72-6D, Vecuronium, polypeptide conjugates 50851-57-5D, polypeptide conjugates 51321-79-0D, Sparfosic acid, polypeptide conjugates 51322-75-9D, Tizanidine, polypeptide conjugates 51384-51-1D, Metoprolol, polypeptide conjugates 52232-67-4D, Teriparatide, polypeptide conjugates 52757-95-6D, Sevelamer, polypeptide conjugates 53179-11-6D, Loperamide, polypeptide conjugates 53230-10-7D, Mefloquine, polypeptide conjugates 54024-22-5D, Desogestrel, polypeptide conjugates 54182-58-0D, Sucralfate, polypeptide conjugates 55142-85-3D, Ticlopidine, polypeptide conjugates 56211-40-6D, Torsemide, polypeptide conjugates 59122-46-2D, Misoprostol, polypeptide conjugates 61477-96-1D, Piperacillin, polypeptide conjugates 61512-21-8D, Thymosin, polypeptide conjugates 61869-08-7D, Paroxetine, polypeptide conjugates 63590-64-7D, Terazosin, polypeptide conjugates 63675-72-9D, Nisoldipine, polypeptide conjugates 65271-80-9D, Mitoxantrone, polypeptide conjugates 65807-02-5D, Goserelin, polypeptide conjugates 66085-59-4D, Nimodipine, polypeptide conjugates 66104-22-1D, Pergolide, polypeptide conjugates 66357-35-5D, Ranitidine, polypeptide conjugates 68562-41-4D, Mecasermin, polypeptide conjugates 68693-11-8D, Modafinil, polypeptide conjugates 70458-96-7D, Norfloxacin, polypeptide conjugates 73590-58-6D, Omeprazole, polypeptide conjugates 74381-53-6D, Leuprolide acetate, polypeptide conjugates 75330-75-5D, Lovastatin, polypeptide conjugates 75970-99-9D, Norastemizole, polypeptide conjugates 76470-66-1D, Loracarbef, polypeptide conjugates 76547-98-3D, Lisinopril, polypeptide conjugates 76963-41-2D, Nizatidine, polypeptide conjugates 79517-01-4D, Octreotide acetate, polypeptide conjugates 79617-96-2D, Sertraline, polypeptide conjugates 79794-75-5D, Loratidine, polypeptide conjugates 79902-63-9D, Simvastatin, polypeptide conjugates 81093-37-0D,

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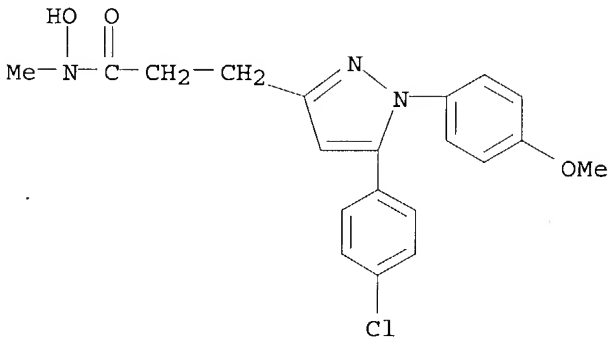
polypeptide conjugates 148883-56-1D, Tifacogin, polypeptide conjugates 151319-34-5D, Zaleplon, polypeptide conjugates 153168-05-9D, Pleconaril, polypeptide conjugates 154039-60-8D, Marimastat, polypeptide conjugates 155141-29-0D, Rosiglitazone maleate, polypeptide conjugates 155213-67-5D, Ritonavir, polypeptide conjugates 158966-92-8D, Montelukast, polypeptide conjugates 159989-65-8D, Nelfinavir mesylate, polypeptide conjugates **162011-90-7D**, Rofecoxib, polypeptide conjugates 166089-32-3D, Lintuzumab, polypeptide conjugates 171228-49-2D, Posaconazole, polypeptide conjugates 171599-83-0D, Sildenafil citrate, polypeptide conjugates 180288-69-1D, Trastuzumab, polypeptide conjugates **181695-72-7D**, Valdecoxib, polypeptide conjugates 188039-54-5D, Palivizumab, polypeptide conjugates 192329-42-3D, Prinomastat, polypeptide conjugates 193079-69-5D, Tabimorelin, polypeptide conjugates 201341-05-1D, Tenofovir disoproxil, polypeptide conjugates
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel pharmaceuticals comprising drug conjugates with polypeptide carriers)

IT **103475-41-8D**, Tepoxalin, polypeptide conjugates
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel pharmaceuticals comprising drug conjugates with polypeptide carriers)

RN 103475-41-8 HCAPLUS

CN 1H-Pyrazole-3-propanamide, 5-(4-chlorophenyl)-N-hydroxy-1-(4-methoxyphenyl)-N-methyl- (9CI) (CA INDEX NAME)



IT **103475-41-8D**, Tepoxalin, polypeptide conjugates
121584-18-7D, Valspodar, polypeptide conjugates
162011-90-7D, Rofecoxib, polypeptide conjugates
181695-72-7D, Valdecoxib, polypeptide conjugates
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel pharmaceuticals comprising drug conjugates with polypeptide carriers)

L199 ANSWER 7 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:750331 HCAPLUS
DOCUMENT NUMBER: 139:62535
TITLE: Rate-Limited Steps of Human Oral Absorption and QSAR Studies
AUTHOR(S): Zhao, Yuan H.; Abraham, Michael H.; Le, Joelle; Hersey, Anne; Luscombe, Chris N.; Beck, Gordon; Sherborne, Brad; Cooper, Ian
CORPORATE SOURCE: Department of Chemistry, University College London, London, WC1H 0AJ, UK
SOURCE: Pharmaceutical Research (2002), 19(10), 1446-1457

CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Purpose. To classify the dissoln. and diffusion rate-limited drugs and establish quant. relationships between absorption and mol. descriptors. Methods. Absorption consists of kinetic transit processes in which dissoln., diffusion, or perfusion processes can become the rate-limited step. The absorption data of 238 drugs have been classified into either dissoln. or diffusion rate-limited based on an equilibrium method developed from solubility, dose, and percentage of absorption. A nonlinear absorption model derived from first-order kinetics has been developed to identify the relationship between percentage of drug absorption and mol. descriptors. Results. Regression anal. was performed between percentage of absorption and mol. descriptors. The descriptors used were ClogP, mol. polar surface area, the number of hydrogen-bonding acceptors and donors, and Abraham descriptors. Good relationships were found between absorption and Abraham descriptors or ClogP. Conclusions. The absorption models can predict the following three BCS (Biopharmaceutics Classification Scheme) classes of compds.: class I, high solubility and high permeability; class III, high solubility
and low permeability; class IV, low solubility and low permeability. The absorption models overpredict the absorption of class II, low solubility and high permeability compds. because dissoln. is the rate-limited step of absorption.

CC 1-2 (Pharmacology)

IT 50-02-2, Dexamethasone 50-22-6, Corticosterone 50-23-7, Hydrocortisone 50-24-8, Prednisolone 50-47-5, Desipramine 50-49-7, Imipramine 50-78-2, Acetylsalicylic acid 50-81-7, Ascorbic acid, biological studies 51-34-3, Scopolamine 51-52-5, Propylthiouracil 51-55-8, Atropine 52-01-7, Spironolactone 52-53-9, Verapamil 53-86-1, Indomethacin 54-11-5, Nicotine 54-31-9, Furosemide 54-85-3, Isoniazid 56-40-6, Glycine, biological studies 56-54-2, Quinidine 56-75-7, Chloramphenicol 57-27-2, Morphine, biological studies 57-41-0, Phenytoin 57-63-6, Ethynylestradiol 57-83-0, Progesterone, biological studies 57-92-1, Streptomycin, biological studies 58-08-2, Caffeine, biological studies 58-15-1, Aminopyrine 58-22-0, Testosterone 58-55-9, Theophylline, biological studies 58-93-5, Hydrochlorothiazide 58-94-6, Chlorothiazide 59-05-2, Methotrexate 59-67-6, Nicotinic acid, biological studies 59-92-7, Levodopa, biological studies 60-80-0, Antipyrine 61-33-6, Benzylpenicillin, biological studies 61-75-6, Bretylium tosylate 64-77-7, Tolbutamide 68-41-7, Cycloserine 69-53-4, Ampicillin 69-65-8, Mannitol 69-72-7, Salicylic acid, biological studies 74-55-5, Ethambutol 76-57-3, Codeine 76-99-3, Methadone 81-07-2, Saccharin 81-81-2, Warfarin 83-43-2, Methylprednisolone 87-08-1, Phenoxymethylpenicillin 97-77-8, Disulfiram 99-66-1, Valproic acid 103-90-2, Acetaminophen 104-06-3, Thiacetazone 114-07-8, Erythromycin 125-28-0, Dihydrocodeine 154-21-2, Lincomycin 300-62-9, Amphetamine 427-51-0, Cyproterone acetate 439-14-5, Diazepam 465-65-6, Naloxone 508-77-0, Cymarin 512-69-6, Raffinose 525-66-6, Propranolol 555-30-6, Methyldopa 586-06-1, Metaproterenol 599-79-1, Sulfasalazine 604-75-1, Oxazepam 630-60-4, Ouabain 637-07-0, Clofibrate 657-24-9, Metformin 738-70-5, Trimethoprim 797-63-7, Levonorgestrel 848-75-9, Lormetazepam 1088-11-5, Nordiazepam 1156-05-4, Phenglutarimide 1197-18-8, Tranexamic acid 1225-20-3, Iothalamatesodium 1397-89-3, Amphotericin b 1404-04-2, Neomycin 1812-30-2, Bromazepam 2165-19-7, Guanoxan 2609-46-3, Amiloride 3056-17-5, Stavudine 3375-50-6, Mercaptoethanesulfonic acid 3930-20-9, Sotalol 4205-90-7, Clonidine 4428-95-9, Foscarnet 4618-18-2, Lactulose 5051-62-7, Guanabenz

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97240-79-4, Topiramate 98048-97-6, Fosinopril 99614-02-5, Ondansetron
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RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rate-limited steps of human oral absorption and QSAR studies)

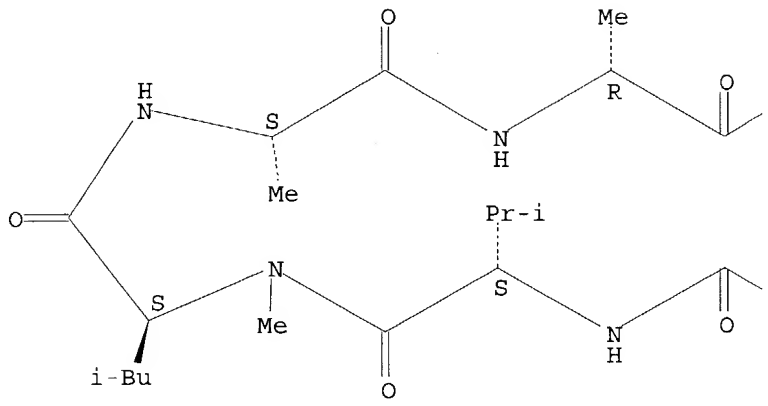
IT **59865-13-3**, Cyclosporin
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rate-limited steps of human oral absorption and QSAR studies)

RN 59865-13-3 HCAPLUS

CN Cyclosporin A (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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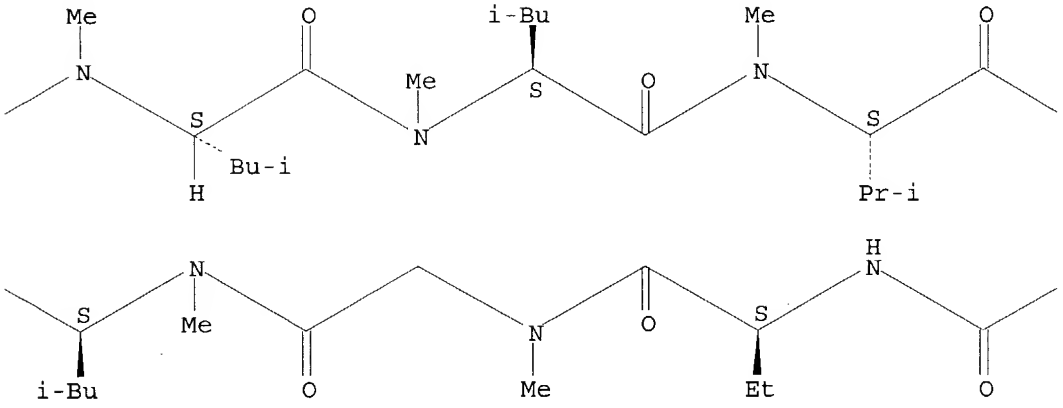

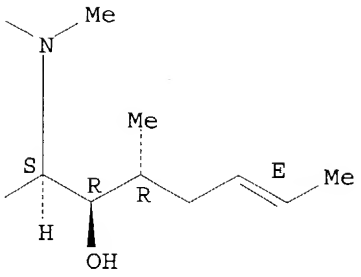

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120210-48-2, Tenidap
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rate-limited steps of human oral absorption and QSAR studies)
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L199 ANSWER 8 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:594844 HCAPLUS
DOCUMENT NUMBER: 137:140518
TITLE: Preparation of thiazolyl-, oxazolyl-, pyrrolyl-, and imidazolyl- acid amide derivatives as inhibitors of phosphodiesterase IV isozymes
INVENTOR(S): Marfat, Anthony; McKechney, Michael William
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 249 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002060898	A1	20020808	WO 2001-IB2728	20011224
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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US 2002123520	A1	20020905	US 2002-62145	20020131
US 6559168	B2	20030506		

US 2003130254	A1	20030710	US 2002-300959		20021120
US 2003186974	A1	20031002	US 2002-300950		20021120
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OTHER SOURCE(S): MARPAT 137:140518

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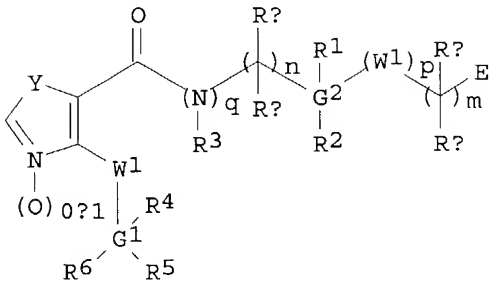

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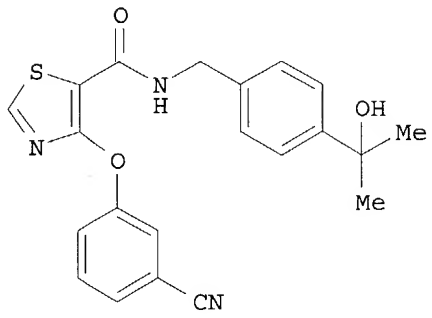

II

AB Title compds. I [wherein p = 0-1; q = 0-1; provided that when q = 0, n = 2; m = 0-3; n = 1-2; W1 and W2 = independently O, SO0-2, or NR3; or W2 = (un)substituted methylene; Y = SO0-2, O, NO0-1, NR3, or (un)substituted methylene; ; RA and RB = independently H, F, CF3, alkyl, or (un)substituted cycloalkyl, Ph, or benzyl; or when m = 1, CRARB = (un)substituted spiro; RC and RD have the same meaning as RA and RB except that one of them must be H; R1 and R2 = H, F, Cl, CN, NO2, (fluoro)alkyl, alkynyl, alkoxy, phenoxy, carbamoyl, etc.; R3 = H, alkyl, Ph, benzyl, alkoxy, phenoxy, etc.; R4, R5, and R6 = H, F, Cl, and (un)substituted (cyclo)alkyl, alkenyl, alkynyl, Ph, benzyl, pyridyl, alkoxy, phenoxy, acyl, carboxy, CN, NO2, carbamoyl, ureido, (hetero)aryl, etc.; G1 and G2 = independently (un)saturated carbocyclyl or heterocyclyl; E = (un)substituted carboxy, carbamoyl, acyl, hydroxyalkyl, cyanoalkyl, acylamino, ureido, amino, heterocyclyl, etc.] were prepared as inhibitors of PDE4 (no data). For example, 4-(3-cyanophenoxy)thiazole-5-carboxylic acid was treated with 2-(4-aminomethylphenyl)propan-2-ol in the presence of EDCl and HOBT in DMF to give the thiazolamide II. I are useful in the treatment of diseases regulated by the activation and degranulation of eosinophils, especially asthma, chronic bronchitis, and chronic obstructive pulmonary disease (no data). In addition, I may be used in combination therapy with a wide variety of

other therapeutic agents.
IC ICM C07D417-12
ICS A61P011-06; A61P029-00; C07D277-56; A61K031-427
CC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
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(combination therapy with PDE4 inhibitors; preparation of thiazolyl-, oxazolyl-, pyrrolyl-, and imidazolyl- acid amide derivs. as inhibitors of PDE4 isoenzymes)
IT **59865-13-3**, Cyclosporine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy with PDE4 inhibitors; preparation of thiazolyl-, oxazolyl-, pyrrolyl-, and imidazolyl- acid amide derivs. as inhibitors of PDE4 isoenzymes)
RN 59865-13-3 HCAPLUS
CN Cyclosporin A (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

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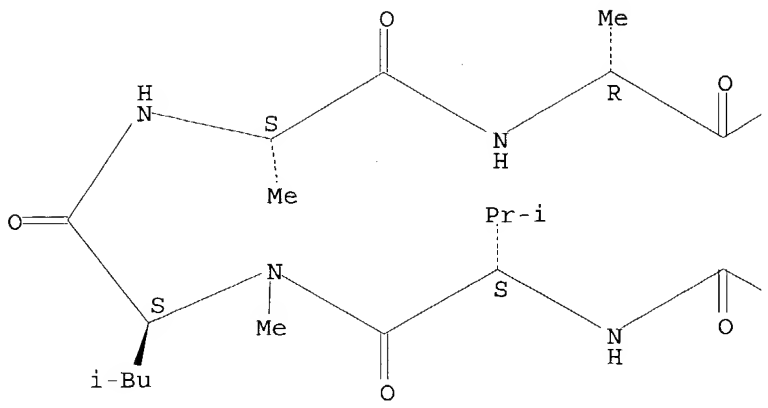

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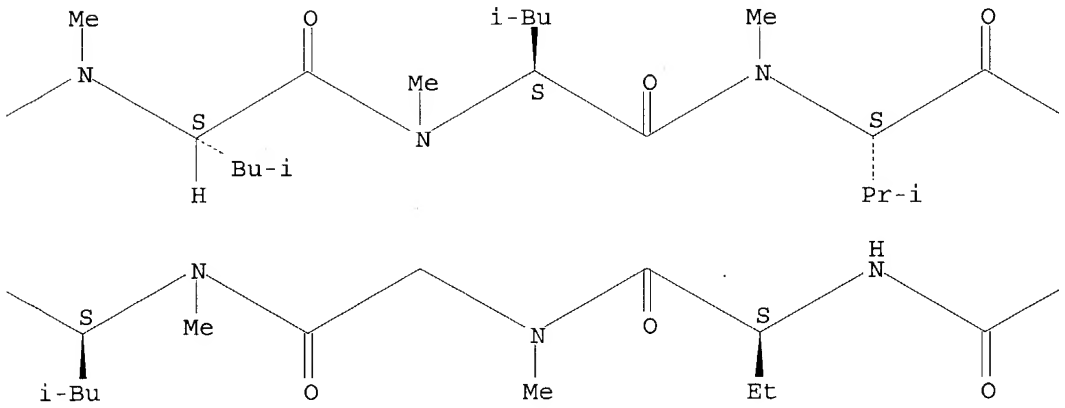

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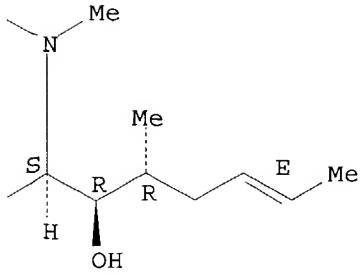

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RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy with PDE4 inhibitors; preparation of thiazolyl-, oxazolyl-, pyrrolyl-, and imidazolyl- acid amide derivs. as inhibitors of PDE4 isoenzymes)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L199 ANSWER 9 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:594842 HCAPLUS
DOCUMENT NUMBER: 137:154859
TITLE: Preparation of carbamoyl-substituted pyridinyl aryl ether derivatives as inhibitors of phosphodiesterase IV isozymes
INVENTOR(S): Chambers, Robert James; Magee, Thomas Victor; Marfat, Anthony
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 285 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002060896	A1	20020808	WO 2001-IB2726	20011224
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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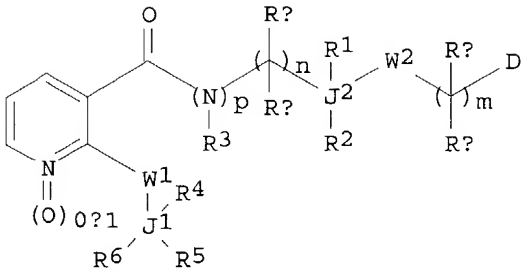
JP 2004518689	T2	20040624	JP 2002-561464	20011224
US 2003027845	A1	20030206	US 2002-66503	20020131
NO 2003003399	A	20030925	NO 2003-3399	20030730

PRIORITY APPLN. INFO.: US 2001-265304P P 20010131
WO 2001-IB2726 W 20011224

OTHER SOURCE(S): MARPAT 137:154859
GI



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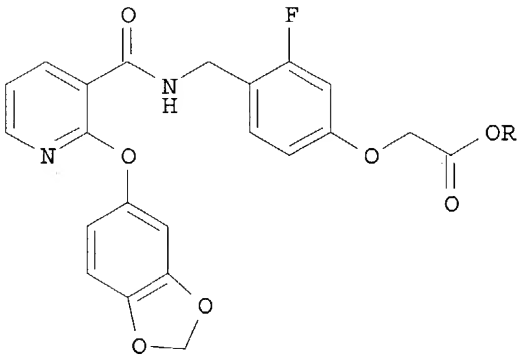


II

AB Title compds. compds. I [wherein p = 0-1, provided that when p = 0, n = 2; m = 1-3; n = 1-2; W1 and W2 = independently O, S(O)0-2, or NR3; Y = =C(R1a) or N(O)0-1; R1a = H, F, Cl, CN, NO2, (fluoro)alkyl, alkynyl, fluoroalkoxy, OR16, or (un)substituted carbamoyl; RA and RB = independently H, F, CF3, or (un)substituted (cyclo)alkyl, Ph, or benzyl; or CRARB = spiro moiety; RC and RD = the same as RA and RB except that one of them must be H; R1 and R2 = independently H, F, Cl, CN, NO2, (fluoro)alkyl, alkynyl, OR16, or (un)substituted carbamoyl; R3 = H, alkyl, Ph, benzyl, or OR16; R4, R5 and R6 = independently H, F. Cl, alkynyl, R16, OR16, SO0-2R16, COR16, CO2R16, OCOR16, CN, NO2, (un)substituted carbamoyl(oxy), ureido, carboximidoyl, aryl, heterocyclyl, etc.; or R5 and R6 taken together with the atoms to which they are attached = (hetero)cyclyl; J1 and J2 = independently (un)substituted, (un)saturated monocyclic or fused polycyclic ring; D = (un)substituted carboxy, carbamoyl, acyl, hydroxy(alkyl), cyano(alkyl), etc.; R16 = H or (un)substituted (cyclo)alkyl, alkenyl, Ph, benzyl, or pyridyl] were prepared as inhibitors of PDE4 (no data). For example, 2-(benzo[1,3]dioxol-5-yloxy)nicotinic acid was coupled with (4-aminomethyl-3-fluorophenoxy)acetic acid Me ester in the presence of 1-hydroxybenzotriazole•H2O and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide•HCl in DMF/CH2Cl2 to give the pyridinecarboxamide II (R = Me) in 38% yield. Saponification using aqueous LiOH in THF and MeOH afforded the desired acid II (R = OH) in 21% yield. I are useful in the treatment of diseases regulated by the activation and degranulation of eosinophils, especially asthma, chronic bronchitis, and chronic obstructive pulmonary disease (no data). In addition, I may be used in combination therapy with a wide variety of other therapeutic agents.

IC ICM C07D405-12
ICS A61K031-44; A61P011-06; A61P029-00

CC 27-16 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

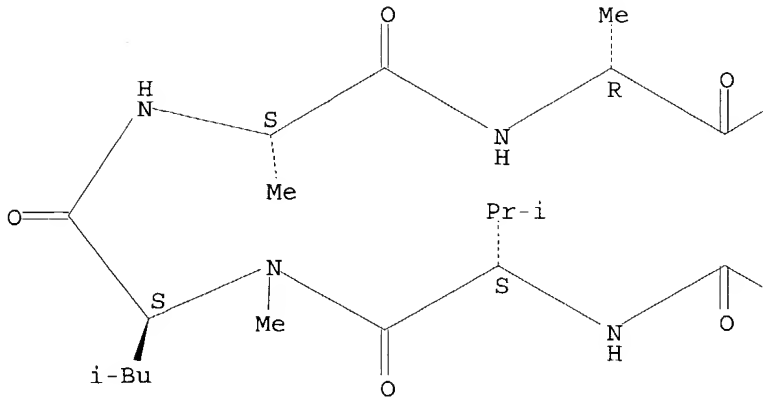
IT 50-24-8, Prednisolone 53-03-2, Prednisone 57-22-7, Vincristine 57-66-9, Probenecid 57-96-5, Sulfinpyrazone 58-55-9, Theophylline, biological studies 59-05-2, Methotrexate 59-42-7, Phenylephrine 64-86-8, Colchicine 76-25-5, Triamcinolone acetonide 90-82-4, Pseudoephedrine 101-40-6, Propylhexedrine 113-92-8, Chlorpheniramine 128-39-2D, 2,6-Di-tert-butylphenol, hydrazone derivs. 315-30-0, Allopurinol 317-34-0, Aminophylline 404-86-4, Capsaicin 446-86-6, Azathioprine 522-48-5, Tetrahydrozoline hydrochloride 550-99-2, Naphazoline hydrochloride 586-06-1, Metaproterenol 865-21-4, Vinblastine 1218-35-5, Xylometazoline hydrochloride 2315-02-8, Oxymetazoline hydrochloride 3198-07-0 3385-03-3, Flunisolide 3562-84-3, Benzbromarone 5534-09-8, Beclomethasone dipropionate 6339-87-3D, Thiophene-2-sulfonamide, derivs. 7440-57-5D, Gold, aurothio derivs. 7683-59-2, Isoproterenol 9004-08-4D, Cathepsin, derivs. 14838-15-4, Phenylpropanolamine 15826-37-6, Sodium cromoglycate 18559-94-9, Albuterol 22254-24-6, Ipratropium bromide 23031-25-6, Terbutaline 28797-61-7, Pirenzepine 30286-75-0, Oxitropium bromide 30392-40-6, Bitolterol 38677-81-5, Pirbuterol 51333-22-3, Budesonide 58581-89-8, Azelastine **59865-13-3**, Cyclosporine 68844-77-9, Astemizole 73573-87-2, Formoterol 75706-12-6, Leflunomide 79794-75-5, Loratadine 80474-14-2, Fluticasone propionate 80880-90-6, Telenzepine 83799-24-0, Fexofenadine 83869-56-1, Granulocyte-macrophage colony-stimulating factor 83881-51-0, Cetirizine 83919-23-7, Mometasone furoate 89365-50-4, Salmeterol **93211-49-5**, L-651392 96566-25-5, Ablukast 100643-71-8, Desloratadine 103177-37-3, Pranlukast **103475-41-8**, Tepoxalin 106096-93-9, Basic fibroblast growth factor 107753-78-6, Zafirlukast **111406-87-2**, Zileuton **118414-82-7**, MK-886 120128-20-3, RG-12525 120443-16-5, Verlukast 126544-47-6, Ciclesonide **128253-31-6**, BAY x 1005 128312-51-6 136310-93-5, Tiotropium bromide **140841-32-3 141579-54-6**, Fenleuton **141579-87-5** 143538-27-6, BAY x 7195 **147030-01-1**, MK-591 147398-01-4, CGS-25019c 147432-77-7, Ontazolast 151581-24-7, Iralukast **154355-76-7**, ABT-761 **158930-07-5**, L-739010 158966-92-8, Montelukast **162011-90-7**, Rofecoxib 162750-10-9, SB-210661 168154-07-2, L-746530 170277-31-3, Infliximab 171964-73-1, ZD-0892 174636-32-9, Talnetant 185243-69-0, Etanercept 202415-99-4 204974-93-6, BIIL 260 257892-34-5, D 4418 331731-18-1, D 2E7 346735-24-8, BIIL 284 350610-64-9, NKP-608C 446023-33-2, UT 77
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy with PDE4 inhibitors; preparation of carbamoyl-substituted pyridinyl aryl ether derivs. as inhibitors of PDE4 isoenzymes)

IT **59865-13-3**, Cyclosporine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy with PDE4 inhibitors; preparation of carbamoyl-substituted pyridinyl aryl ether derivs. as inhibitors of PDE4 isoenzymes)

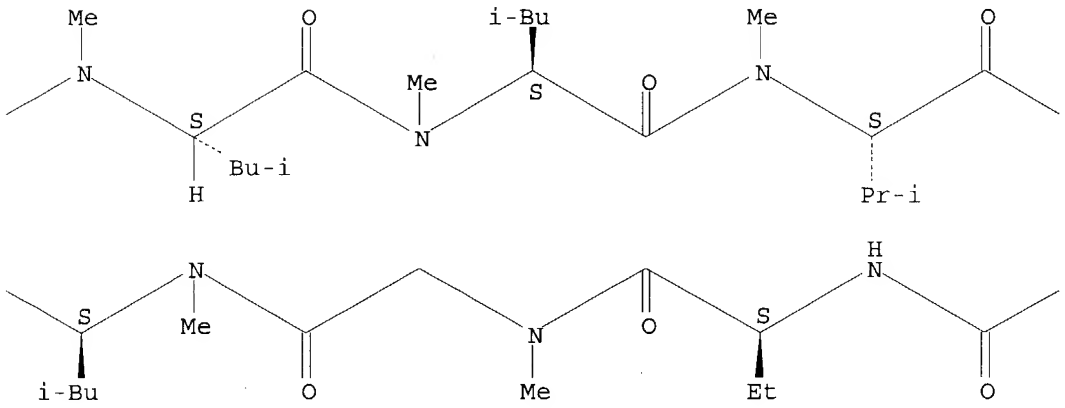
RN 59865-13-3 HCAPLUS
CN Cyclosporin A (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



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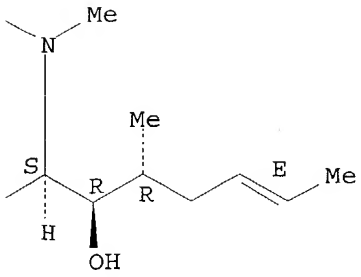

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118414-82-7, MK-886 **128253-31-6**, BAY x 1005
140841-32-3 141579-54-6, Fenleuton **141579-87-5**
147030-01-1, MK-591 **154355-76-7**, ABT-761
158930-07-5, L-739010 **162011-90-7**, Rofecoxib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy with PDE4 inhibitors; preparation of carbamoyl-substituted pyridinyl aryl ether derivs. as inhibitors of PDE4 isoenzymes)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L199 ANSWER 10 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:594822 HCAPLUS
DOCUMENT NUMBER: 137:154857
TITLE: Preparation of nicotinamide biaryl derivatives as inhibitors of PDE4 isozymes
INVENTOR(S): Chambers, Robert James; Magee, Thomas Victor; Marfat, Anthony
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 224 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002060875	A1	20020808	WO 2001-IB2341	20011206
WO 2002060875	C1	20030731		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1355884	A1	20031029	EP 2001-273556	20011206
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
EE 200300360	A	20031215	EE 2003-360	20011206
BR 2001016852	A	20040225	BR 2001-16852	20011206
JP 2004520386	T2	20040708	JP 2002-561026	20011206
US 2002193612	A1	20021219	US 2002-62813	20020131
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US 2004048903	A1	20040311	US 2003-613988	20030702
NO 2003003397	A	20030919	NO 2003-3397	20030730

PRIORITY APPLN. INFO.: US 2001-265492P P 20010131
WO 2001-IB2341 W 20011206
US 2002-62813 A3 20020131
OTHER SOURCE(S): MARPAT 137:154857
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I; g = 0-1; j = 0-1; provided that when j = 0, n must be 2; k = 0-1; m = 0-2; n = 1-2; W1 = 0, SOt (t = 0-2), NR3; W2 = OCR9R10, or absent; Y = CR1, NOk (k = 0-1); R9, R10 = H, F, CF3, etc.; or R9 and R10 are taken together, but only in the case where m = 1, to form a spiro moiety; R7, R8 have the same meaning as R9, R10 except that one of them must be H; R1, R2 = H, F, Cl, etc.; R3 = H, alkyl, Ph, etc.; R4-R6 = H, F, Cl, etc.; Q1 = Ph, benzodioxyl, etc.; Q2 = biaryl moiety], useful as inhibitors of PDE4 in the treatment of diseases regulated by the activation and degranulation of eosinophils, especially asthma, chronic bronchitis, and chronic obstructive pulmonary disease, were prepared E.g., a multi-step synthesis of the amide II, starting from Me 3-bromobenzoate and 4-formylbenzeneboronic acid, was given. Compds. I showed anti-inflammatory activity at 0.0001 μM to 20.0 μM in whole blood assay for LTE4.

IC ICM C07D213-82
ICS C07D405-12; A61K031-44; A61P011-06; A61P029-00

CC 27-16 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 10

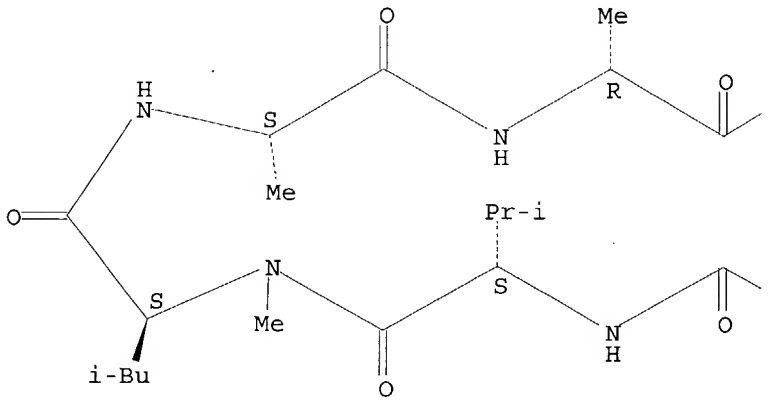
IT 57-22-7, Vincristine 57-66-9, Probenecid 57-96-5, Sulfinpyrazone 58-55-9, Theophylline, biological studies 59-05-2, Methotrexate 59-42-7, Phenylephrine 64-86-8, Colchicine 76-25-5, Triamcinolone acetonide 90-82-4, Pseudoephedrine 101-40-6, Propylhexedrine 113-92-8, Chlorpheniramine 315-30-0, Allopurinol 317-34-0, Aminophylline 446-86-6, Azathioprine 522-48-5, Tetrahydrozoline hydrochloride 550-99-2, Naphazoline hydrochloride 586-06-1, Orciprenaline 865-21-4, Vinblastine 1218-35-5, Xylometazoline hydrochloride 1397-89-3, Amphotericin B 1404-26-8, Polymyxin B 2315-02-8, Oxymetazoline hydrochloride 3198-07-0 3385-03-3, Flunisolide 3562-84-3, Benzbromarone 5534-09-8, Beclomethasone dipropionate 7440-57-5D, Gold, derivs. 7683-59-2, Isoprenaline 9004-08-4, Cathepsin 14838-15-4, Phenylpropanolamine 15826-37-6, Sodium cromoglycate 18559-94-9, Salbutamol 22254-24-6, Ipratropium bromide 22916-47-8, Miconazole 23031-25-6, Terbutaline 23593-75-1, Clotrimazole 27220-47-9, Econazole 30392-41-7, Bitolterol mesylate 38677-81-5, Pirbuterol 51333-22-3, Budesonide 58581-89-8, Azelastine **59865-13-3**, Cyclosporine 65277-42-1, Ketoconazole 68844-77-9, Astemizole 73573-87-2, Formoterol 75706-12-6, Leflunomide 79794-75-5, Loratadine 80474-14-2, Fluticasone propionate 83799-24-0, Fexofenadine 83881-51-0, Cetirizine 83919-23-7, Mometasone furoate 86386-73-4, Fluconazole 89365-50-4, Salmeterol **93211-49-5**, L-651392 96566-25-5, Ablukast 100643-71-8, Desloratadine 103177-37-3, Pranlukast **103475-41-8**, Tepoxalin 107753-78-6, Zafirlukast **111406-87-2**, Zileuton **118414-82-7**, MK-886 120128-20-3, RG-12525 120443-16-5, Verlukast 126544-47-6, Ciclesonide **128253-31-6**, BAY X 1005 **140841-32-3**, ZD 2138 **141579-54-6**, Fenleuton 143538-27-6, BAY x 7195 **147030-01-1**, MK-591 147398-01-4, CGS-25019c 147432-77-7, Ontazolast 151581-24-7, Iralukast **154355-76-7**, ABT-761 **158930-07-5**, L-739010 158966-92-8, Montelukast **162011-90-7**, Rofecoxib 162750-10-9, SB-210661 168154-07-2, L-746530 170277-31-3, Infliximab 185243-69-0, Etanercept 257892-34-5, D 4418 331731-18-1, D 2E7
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in combination with; preparation of biaryl nicotinamides as inhibitors of PDE4 isoenzymes)

IT **59865-13-3**, Cyclosporine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in combination with; preparation of biaryl nicotinamides as inhibitors of PDE4 isoenzymes)

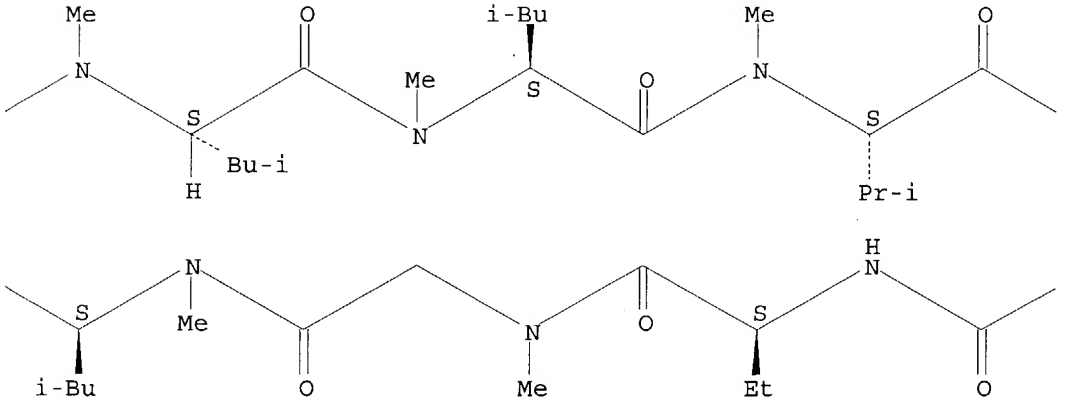
RN 59865-13-3 HCAPLUS
CN Cyclosporin A (9CI) (CA INDEX NAME)

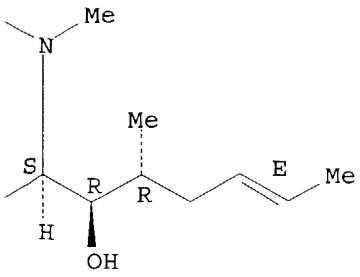
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B





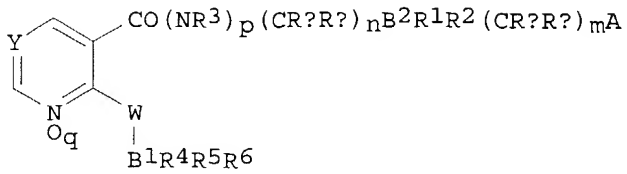
IT **59865-13-3**, Cyclosporine **93211-49-5**, L-651392
103475-41-8, Tepoxalin **111406-87-2**, Zileuton
118414-82-7, MK-886 **128253-31-6**, BAY X 1005
140841-32-3, ZD 2138 **141579-54-6**, Fenleuton
147030-01-1, MK-591 **154355-76-7**, ABT-761
158930-07-5, L-739010 **162011-90-7**, Rofecoxib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in combination with; preparation of biaryl nicotinamides as inhibitors of PDE4 isoenzymes)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L199 ANSWER 11 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:591707 HCAPLUS
DOCUMENT NUMBER: 137:140509
TITLE: Preparation of nicotinamides and mimetics as inhibitors of phosphodiesterase IV isozymes
INVENTOR(S): Chambers, Robert J.; Magee, Thomas V.; Marfat, Anthony
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 180 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1229034	A1	20020807	EP 2002-250202	20020111
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002111495	A1	20020815	US 2002-62811	20020131
BR 2002000250	A	20021008	BR 2002-250	20020131

PRIORITY APPLN. INFO.: US 2001-265240P P 20010131
US 1997-43403P P 19970404
US 1998-105120P P 19981021
OTHER SOURCE(S): MARPAT 137:140509
GI



I

AB Title compds. [I; p, q = 0, 1; m = 0-2; n = 1, 2; A = CO2R7, CONR9CO2R7, CONR7R9, OP(O)(OH)2, SO3H, acylsulfonamido, etc.; W = O, S, SO, SO2, NR3; Y = N, NO, CR11; R1, R2 = H, F, Cl, cyano, NO2, alkyl, alkynyl, fluoroalkyl, etc.; R3 = H, alkyl, Ph, PhCH2, etc.; R4-R6 = H, F, Cl, alkynyl, cyano, NO2, etc.; R7 = H, (substituted) alkyl, alkenyl, alkynyl; R9 = H, alkyl, cycloalkyl, Ph, PhCH2, pyridyl, etc.; R11 = H, F, Cl, cyano, NO2, alkyl, alkynyl, fluoroalkyl, fluoroalkoxy, etc.; Ra, Rb = H, F, CF3, alkyl, (substituted) cycloalkyl, Ph, PhCH2; B1, B2 = 3-7 membered (hetero)cyclyl, 7-12 membered poly(hetero)cyclyl; pairs of variables may form rings; with provisos], were prepared (no data). Thus, Me 2-[4-[[[2-(benzo[1,3]dioxol-5-yloxy)pyridine-3-carbonyl]amino]methyl]phenyl]-2-methylpropionate was suspended in Me3COH. Aqueous NaOH was added to the suspension, and the reaction mixture was refluxed 1 h to give 2-[4-[[[2-(benzo[1,3]dioxol-5-yloxy)pyridine-3-carbonyl]amino]methyl]phenyl]-2-methylpropionic acid.

IC ICM C07D401-12
ICS C07D405-12; C07D405-14; C07D413-12; C07D213-64; A61K031-44; A61K031-455; A61P029-00; A61P037-08; A61P011-06

CC 28-5 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 27

IT 50-24-8, Prednisolone 57-22-7, Vincristin 57-66-9, Probenecid 57-96-5, Sulfinpyrazone 58-55-9, Theophylline, biological studies 59-42-7, Phenylephrine 64-86-8, Colchicine 76-25-5, Triamcinolone acetonide 84-22-0, Tetrahydrozoline 90-82-4, Pseudoephedrine 101-40-6, Propylhexedrine 113-92-8, Chlorpheniramine 315-30-0, Allopurinol 317-34-0, Aminophyllin 404-86-4, Capsaicin 586-06-1, Orciprenaline 835-31-4, Naphazoline 865-21-4, Vinblastine 1218-35-5, Xylometazoline hydrochloride 1397-89-3, Amphotericin b 1404-26-8, Polymyxin B 1491-59-4, Oxymetazoline 3198-07-0 3385-03-3, Flunisolide 3562-84-3, Benzbromarone 5534-09-8, Beclomethasone dipropionate 7440-57-5D, Gold, aurothio compds. 7683-59-2, Isoproterenol 14838-15-4, Phenylpropanolamine 15826-37-6, Sodium cromoglycate 18559-94-9, Albuterol 22916-47-8, Miconazole 23031-25-6, Terbutaline 23593-75-1, Clotrimazole 27220-47-9, Econazole 28797-61-7, Pirenzepine 30286-75-0, Oxitropium bromide 30392-40-6, Bitolterol 38677-81-5, Pirbuterol 51333-22-3, Budesonide 58581-89-8, Azelastine **59865-13-3**, Cyclosporine 60205-81-4, Ipratropium 65277-42-1, Ketoconazole 68844-77-9, Astemizole 73573-87-2, Formoterol 75706-12-6, Leflunomide 79794-75-5, Loratidine 80880-90-6, Telenzepine 83799-24-0, Fexofenadine 83869-56-1, Granulocyte macrophage colony stimulating factor 83881-51-0, Cetirizine 83919-23-7, Mometasone furoate 86386-73-4, Fluconazole 89365-50-4, Salmeterol 90566-53-3, Fluticasone **93211-49-5**, L-651392 100643-71-8, Desloratadine 103177-37-3, Pranlukast **103475-41-8**, Tepoxalin 106096-93-9, Basic fibroblast growth factor 107753-78-6, Zafirlukast **111406-87-2**, Zileuton **118414-82-7**, Mk-886 120128-20-3, RG-12525 120443-16-5, Verlukast 126544-47-6, Ciclesonide **128253-31-6**, BAY x 1005 136310-93-5, Tiotropium bromide **140841-32-3**, ZD-2138 **141579-54-6**, Fenleuton **141579-87-5**, A 79175 143538-27-6, BAY x 7195 **147030-01-1**

, Mk-591 147398-01-4, CGS-25019c 147432-77-7, Ontazolast
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, L-739010 158966-92-8, Montelukast **162011-90-7**, Rofecoxib
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RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy; preparation of nicotinamides and mimetics as inhibitors of phosphodiesterase IV isoenzymes)

IT **59865-13-3**, Cyclosporine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy; preparation of nicotinamides and mimetics as inhibitors of phosphodiesterase IV isoenzymes)

RN 59865-13-3 HCAPLUS
CN Cyclosporin A (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

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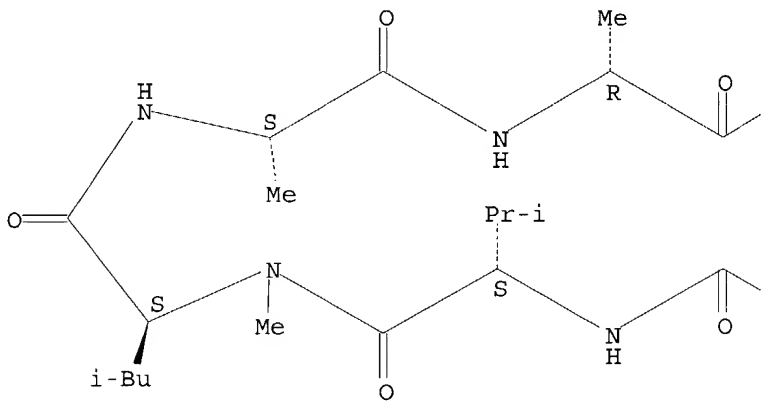

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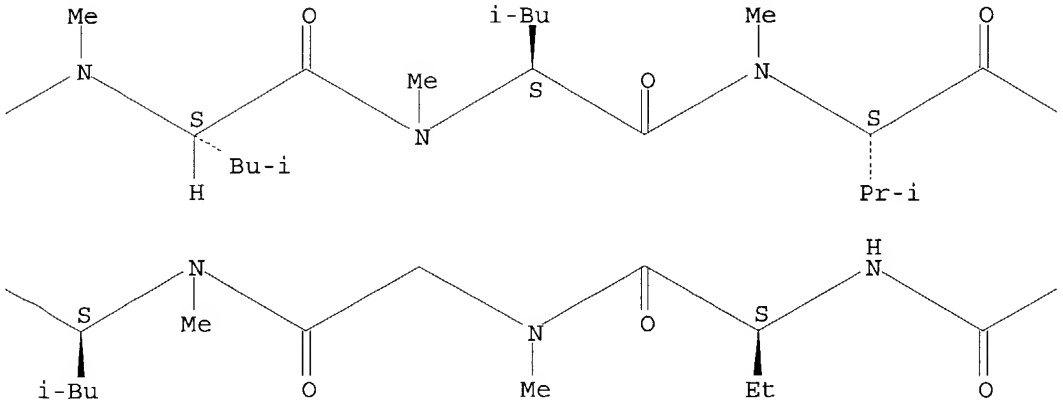

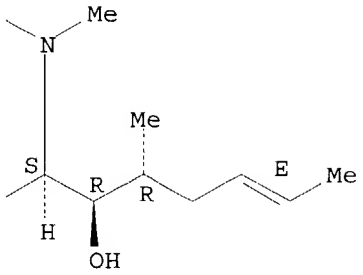

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RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy; preparation of nicotinamides and mimetics as inhibitors of phosphodiesterase IV isoenzymes)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L199 ANSWER 12 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:556104 HCAPLUS
DOCUMENT NUMBER: 137:109489
TITLE: Compositions comprising a polypeptide and an active agent
INVENTOR(S): Piccariello, Thomas; Olon, Lawrence P.; Kirk, Randal J.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 34 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002099013	A1	20020725	US 2001-933708	20010822
US 2004087483	A1	20040506	US 2002-136433	20020502

PRIORITY APPLN. INFO.:

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US 2000-642820 A2 20000822
US 2000-248607P P 20001116
US 2001-933708 A2 20010822

AB Claimed are compns. comprising a polypeptide and an active agent covalently attached to the polypeptide and a method for delivery of an active agent to a patient by administering the composition to the patient. The peptide is a homopolymer of a naturally occurring amino acid or a heteropolymer of two or more naturally occurring amino acids. In an example, (Glu)n-cephalexin was prepared from Glu(OBut)NCA and cephalexin hydrochloride.

IC ICM A61K038-17

NCL 514012000

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 63

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RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a polypeptide and an active agent)

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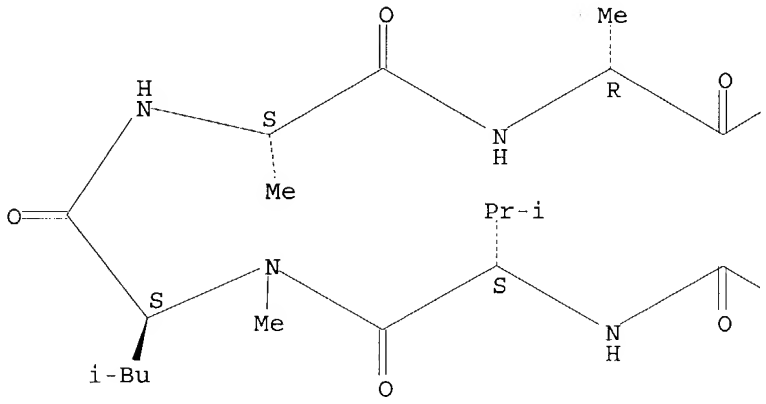
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a polypeptide and an active agent)

IT **59865-13-3**, Cyclosporin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a polypeptide and an active agent)

RN 59865-13-3 HCAPLUS
CN Cyclosporin A (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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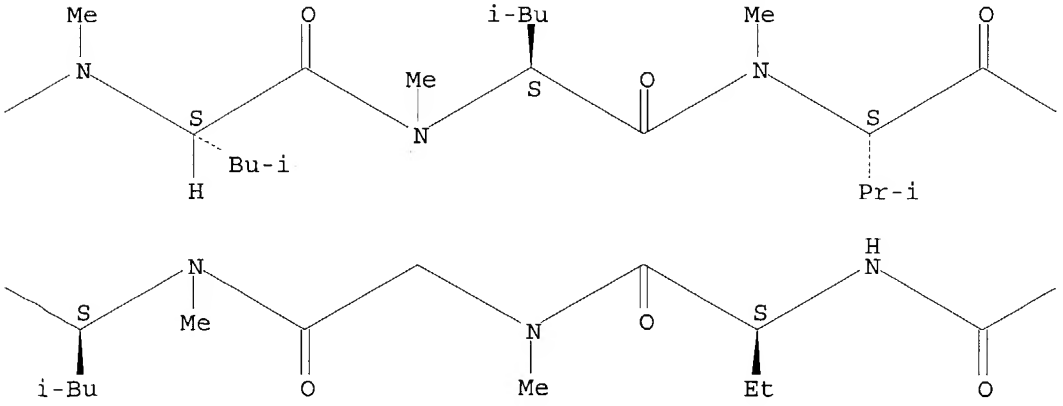

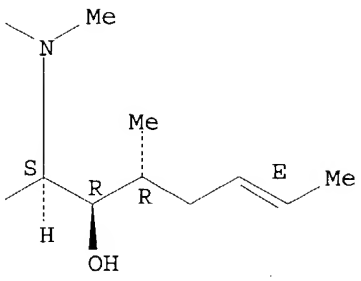

IT **59865-13-3**, Cyclosporin **103475-41-8**, Tepoxalin
121584-18-7, Valspodar **141579-67-1**, A 78773
162011-90-7, Rofecoxib **181695-72-7**, Valdecoxib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a polypeptide and an active agent)

L199 ANSWER 13 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:332011 HCAPLUS
DOCUMENT NUMBER: 136:355482
TITLE: Compositions comprising a polypeptide and an active agent
INVENTOR(S): Piccariello, Thomas; Olon, Lawrence P.; Kirk, Randall J.
PATENT ASSIGNEE(S): New River Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002034237	A1	20020502	WO 2001-US26142	20010822
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 6716452	B1	20040406	US 2000-642820	20000822
AU 2001086599	A5	20020506	AU 2001-86599	20010822
EP 1311242	A1	20030521	EP 2001-966056	20010822
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US 2004127397	A1	20040701	US 2003-727565	20031205

PRIORITY APPLN. INFO.: US 2000-642820 A 20000822
WO 2001-US26142 W 20010822

AB Claimed are compns. comprising a polypeptide and an active agent covalently attached to the polypeptide and a method for delivery of an

active agent to a patient by administering the composition to the patient. The peptide is a homopolymer of a naturally occurring amino acid or a heteropolymer of two or more naturally occurring amino acids. In an example, (Glu)n-cephalexin was prepared from Glu(OBut)NCA and cephalexin hydrochloride.

IC ICM A61K009-14
ICS A61K009-22; A61K009-50; A61K047-42; C07K001-02; C07K001-13

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 63

IT 50-06-6, Phenobarbital, biological studies 50-18-0, Cyclophosphamide 50-35-1, Thalidomide 50-44-2, Mercaptopurine 50-78-2, Acetylsalicylic acid 50-81-7, Vitamin C, biological studies 51-21-8, Fluorouracil 51-61-6, Dopamine, biological studies 51-63-8, Dextroamphetamine sulfate 51-98-9, Norethindrone acetate 52-01-7, Spironolactone 52-24-4, Thiotepa 52-86-8, Haloperidol 53-36-1, Methylprednisolone Acetate 54-31-9, Furosemide 55-63-0, Nitroglycerin 57-63-6, Ethinyl estradiol 58-08-2, Caffeine, biological studies 58-18-4, Methyltestosterone 58-25-3, Chlordiazepoxide 58-33-3, Promethazine hydrochloride 58-55-9, Theophylline, biological studies 58-61-7, Adenosine, biological studies 58-93-5, Hydrochlorothiazide 59-42-7, Phenylephrine 60-54-8, Tetracycline 60-87-7, Promethazine 64-31-3, Morphine Sulfate 67-20-9, Nitrofurantoin 67-92-5, Dicyclomine hydrochloride 68-19-9, Vitamin B12 68-22-4, Norethindrone 71-58-9, Medroxyprogesterone acetate 71-68-1, Hydromorphone hydrochloride 74-79-3, Arginine, biological studies 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-58-4, Ethylmorphine 78-44-4, Carisoprodol 84-02-6, Prochlorperazine maleate 87-08-1, Penicillin V 87-33-2, Isosorbide Dinitrate 89-57-6, Mesalamine 90-82-4, Pseudoephedrine 93-14-1, Guaifenesin 113-45-1, Methylphenidate 113-52-0 113-92-8, Chlorpheniramine maleate 114-07-8, Erythromycin 124-90-3, Oxycodone hydrochloride 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 125-33-7, Primidone 125-71-3, Dextromethorphan 128-13-2, Ursodiol 129-06-6, Warfarin Sodium 132-17-2, Benzatropine methanesulfonate 132-22-9, Chlorpheniramine 143-52-2, Methyldihydromorphinone 143-71-5, Hydrocodone bitartrate 152-11-4, Verapamil hydrochloride 297-76-7, Ethynodiol diacetate 298-46-4, Carbamazepine 298-59-9, Methylphenidate hydrochloride 303-49-1, Clomipramine 315-30-0, Allopurinol 318-98-9, Propranolol Hydrochloride 378-44-9, Betamethasone 379-79-3, Ergotamine Tartrate 437-38-7, Fentanyl 439-14-5, Diazepam 446-86-6, Azathioprine 466-99-9, Hydromorphone 469-62-5, Propoxyphene 509-60-4, Dihydromorphine 514-36-3, Fludrocortisone acetate 541-15-1, Levocarnitine 549-18-8, Amitriptyline hydrochloride 554-13-2, Lithium Carbonate 561-27-3, Diacetylmorphine 595-33-5, Megestrol acetate 604-75-1, Oxazepam 630-93-3, Sodium phenytoin 657-24-9, Metformin 745-65-3, Alprostadil 747-36-4, Hydroxychloroquine sulfate 797-63-7, Levonorgestrel 846-49-1, Lorazepam 846-50-4, Temazepam 894-71-3, Nortriptyline hydrochloride 959-24-0, Sotalol hydrochloride 1134-47-0, Baclofen 1403-66-3, Gentamicin 1404-93-9, Vancomycin hydrochloride 1501-84-4, Rimantadine hydrochloride 1508-65-2, Oxybutynin chloride 1622-61-3, Clonazepam 1665-48-1, Metaxalone 1744-22-5, Riluzole 1951-25-3, Amiodarone 2078-54-8, Propofol 2152-34-3, Pemoline 2375-03-3, Methylprednisolone sodium succinate 4205-91-8 4682-36-4, Orphenadrine citrate 4759-48-2, Isotretinoin 5786-21-0, Clozapine 6202-23-9, Cyclobenzaprine hydrochloride 6493-05-6, Pentoxifylline 6533-00-2, Norgestrel 7280-37-7, Estropipate 7414-83-7, Etidronate disodium 9002-60-2, Adrenocorticotrophic hormone, biological studies 9002-69-1, Relaxin 9005-49-6, Heparin, biological studies 9014-42-0, Thrombopoietin 9039-53-6, Urokinase 9041-08-1, Dalteparin sodium 9041-92-3, .α.1-Protease inhibitor 9080-79-9, Sodium polystyrene sulfonate 10238-21-8, Glyburide 11005-12-2, β-Phytosterol

11056-06-7, Bleomycin 11140-85-5, Glucagon hydrochloride 13311-84-7, Flutamide 13614-98-7, Minocycline hydrochloride 14124-50-6, Hydrochlorothiazide-triamterene mixture 14611-52-0, Selegiline hydrochloride 14838-15-4, Phenylpropanolamine 15307-79-6, Diclofenac sodium 15663-27-1, Cisplatin 15686-71-2, Cephalexin 17140-78-2, Propoxyphene napsylate 17560-51-9, Metolazone 18559-94-9, Albuterol 19767-45-4, Mesna 20537-88-6, Amifostine 20830-75-5, Digoxin 21062-37-3D, analogs 21256-18-8, Oxaprozin 21829-25-4, Nifedipine 22071-15-4, Ketoprofen 23031-32-5, Terbutaline sulfate 25316-40-9, Doxorubicin hydrochloride 25322-68-3, Polyethylene glycol 25332-39-2, Trazodone hydrochloride 25614-03-3, Bromocriptine 26159-34-2, Naproxen sodium 26787-78-0, Amoxicillin 27164-46-1, Cefazolin sodium 27314-97-2, Tirapazamine 28860-95-9, Carbidopa 28981-97-7, Alprazolam 29094-61-9, Glipizide 29354-16-3, Thyronine, iodo- 31677-93-7, Bupropion hydrochloride 32222-06-3, Calcitriol 32780-64-6, Labetalol hydrochloride 33069-62-4, Paclitaxel 33286-22-5, Diltiazem hydrochloride 33419-42-0, Etoposide 33564-30-6, Cefoxitin sodium 34552-83-5, Loperamide hydrochloride 34580-13-7, Ketotifen 35189-28-7, Norgestimate 36282-47-0, Tramadol hydrochloride 36505-84-7, Buspirone 36791-04-5, Ribavirin 37296-80-3, Colestipol hydrochloride 38398-32-2, Ganaxolone 41340-25-4, Etodolac 41575-94-4, Carboplatin 42200-33-9, Nadolol 42617-41-4, Activated protein C 42924-53-8, Nabumetone 49562-28-9, Fenofibrate 49842-07-1, Tobramycin sulfate 50370-12-2, Cefadroxil 50700-72-6, Vecuronium bromide 51321-79-0, Sparfosic acid 51481-61-9, Cimetidine 51773-92-3, Mefloquine hydrochloride 52232-67-4, Teriparatide 53885-35-1, Ticlopidine hydrochloride 53994-73-3, Cefaclor 54024-22-5, Desogestrel 54143-56-5, Flecainide acetate 54182-58-0, Sucralfate 54910-89-3, Fluoxetine 54965-24-1, Tamoxifen citrate 55079-83-9, Acitretin 56180-94-0, Acarbose 56238-63-2, Cefuroxime sodium 57109-90-7, Clorazepate dipotassium 57248-88-1, Pamidronate disodium 57852-57-0, Idarubicin hydrochloride 58579-51-4, Anagrelide hydrochloride 58786-99-5, Butorphanol tartrate 59122-46-2, Misoprostol 59703-84-3, Piperacillin sodium 59729-32-7, Citalopram hydrobromide **59865-13-3**, Cyclosporin 59989-18-3, Eniluracil 60142-96-3, Gabapentin 60205-81-4, Ipratropium 60748-06-3, Gastrin 17 61718-82-9, Fluvoxamine maleate 62288-83-9, Desmopressin acetate 62571-86-2, Captopril 63074-08-8, Terazosin hydrochloride 63675-72-9, Nisoldipine 64221-86-9, Imipenem 64461-82-1, Tizanidine hydrochloride 64485-93-4, Cefotaxime sodium 64544-07-6, Cefuroxime axetil 65277-42-1, Ketoconazole 65646-68-6, Fenretinide 65807-02-5, Goserelin 66085-59-4, Nimodipine 66104-22-1, Pergolide 66357-35-5, Ranitidine 66722-44-9, Bisoprolol 67889-72-9, Acetaminophen-codeine phosphate mixture 67992-58-9, Sodium ioxaglate 68562-41-4, Mecasermin 68693-11-8, Modafinil 68844-77-9, Astemizole 69655-05-6, Didanosine 70458-96-7, Norfloxacin 70476-82-3, Mitoxantrone hydrochloride 72509-76-3, Felodipine 72558-82-8, Ceftazidime 72956-09-3, Carvedilol 73334-07-3, Iopromide 73573-87-2, Formoterol 73590-58-6, Omeprazole 74103-06-3, Ketorolac 74191-85-8, Doxazosin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a polypeptide and an active agent)

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acetate 79794-75-5, Loratadine 79902-63-9, Simvastatin 81098-60-4, Cisapride 81103-11-9, Clarithromycin 81129-83-1, Cilastatin sodium 81131-70-6, Pravastatin sodium 81409-90-7, Cabergoline 81627-83-0, M-CSF 82410-32-0, Ganciclovir 82419-36-1, Ofloxacin 82586-52-5, Moexipril hydrochloride 82586-55-8, Quinapril hydrochloride 82626-48-0, Zolpidem 82640-04-8, Raloxifene hydrochloride 82657-92-9, Prourokinase 82752-99-6, Nefazodone hydrochloride 83015-26-3, Tomoxetine 83881-52-1, Cetirizine hydrochloride 83905-01-5, Azithromycin 83928-66-9, Gepirone hydrochloride 84057-84-1, Lamotrigine 84485-00-7, Sibutramine hydrochloride 84625-61-6, Itraconazole 85650-52-8, Mirtazapine 85721-33-1, Ciprofloxacin 86050-77-3, Gadopentetate dimeglumine 86386-73-4, Fluconazole 86541-74-4, Benazepril hydrochloride 87239-81-4, Cefpodoxime proxetil 87333-19-5, Ramipril 87679-37-6, Trandolapril 90357-06-5, Bicalutamide 90566-53-3, Fluticasone 91374-20-8, Ropinirole hydrochloride 91421-42-0, Rubitecan 91832-40-5, Cefdinir 92134-98-0, Fosphenytoin sodium 92339-11-2, Iodixanol 92665-29-7, Cefprozil 93379-54-5, Esatenolol 93479-97-1, Glimepiride 93957-54-1, Fluvastatin 95233-18-4, Atovaquone 95635-56-6, Ranolazine hydrochloride 95896-08-5, Anaritide 96036-03-2, Meropenem 96829-58-2, Orlistat 96946-42-8, Cisatracurium besylate 97240-79-4, Topiramate 97322-87-7, Troglitazone 97519-39-6, Ceftibuten 98048-97-6, Fosinopril 98319-26-7, Finasteride 98418-47-4, Metoprolol succinate 99300-78-4, Venlafaxine hydrochloride 99614-01-4, Ondansetron hydrochloride 100286-90-6, Irinotecan hydrochloride 100286-97-3, Milrinone lactate 100986-85-4, Levofloxacin **103475-41-8**, Tepoxalin 103577-45-3, Lansoprazole 104227-87-4, Famciclovir 104632-25-9, Pramipexole dihydrochloride 106266-06-2, Risperidone 106392-12-5, Poloxamer 188 106861-44-3, Mivacurium chloride 107007-99-8, Granisetron hydrochloride 107753-78-6, Zafirlukast 111470-99-6, Amlodipine besylate 111974-72-2, Quetiapine fumarate 112108-01-7, Ecopipam 112529-15-4, Pioglitazone hydrochloride 112573-73-6, Ecadotril 112733-06-9, Zenarestat 113427-24-0, Epoetin alfa 114977-28-5, Docetaxel 115956-13-3, Dolasetron mesylate 116539-59-4, Duloxetine 117976-90-6, Rabeprazole sodium 118390-30-0, Interferon alfacon-1 119302-91-9, Rocuronium bromide 119413-54-6, Topotecan hydrochloride 120011-70-3, Donepezil hydrochloride 120066-54-8, Gadoteridol 120202-66-6, Clopidogrel bisulfate 120511-73-1, Anastrozole 120635-74-7, Cilansetron 121032-29-9, Nelarabine 121181-53-1D, PEGylated **121584-18-7**, Valspodar 122111-03-9, Gemcitabine hydrochloride 123122-55-4, Candoxatril 123258-84-4, Itasetron 124584-08-3, Nesiritide 124750-99-8, Losartan potassium 124832-27-5, Valacyclovir hydrochloride 124937-52-6, Tolterodine tartrate 125317-39-7, Vinorelbine tartrate 126544-47-6, Ciclesonide 127254-12-0, Sitafloxacin 127779-20-8, Saquinavir 128298-28-2, Remacemide 128794-94-5, Mycophenolate mofetil 129318-43-0, Alendronate sodium 129580-63-8, Satraplatin 129618-40-2, Nevirapine 129722-12-9, Aripiprazole 130018-77-8, Levocetirizine 130325-35-8, PD 135158 131918-61-1, Paricalcitol 132449-46-8, Lesopitron 132539-06-1, Olanzapine 133107-64-9, Insulin lispro 133737-32-3, Pagoclone 134523-03-8, Atorvastatin calcium 134564-82-2, Befloxatone 134678-17-4, Lamivudine 135062-02-1, Repaglinide 135306-42-2, BW 1555U88 135354-02-8, Xaliproden 137234-62-9, Voriconazole 137281-23-3, Pemetrexed 137862-53-4, Valsartan 138402-11-6, Irbesartan 138531-07-4, Sinapultide 138660-96-5, Sevirumab 139264-17-8, Zolmitriptan 140207-93-8, Pentosan polysulfate sodium **141579-67-1**, A 78773 141732-76-5, Exendin-4 142340-99-6, Adefovir dipivoxil 142373-60-2, Tirofiban hydrochloride 142880-36-2, Ilomastat 143201-11-0, Cerivastatin sodium 143388-64-1, Naratriptan hydrochloride 144980-29-0, Repinotan 145040-37-5, Candesartan cilexetil 145202-66-0, Rizatriptan benzoate 145258-61-3,

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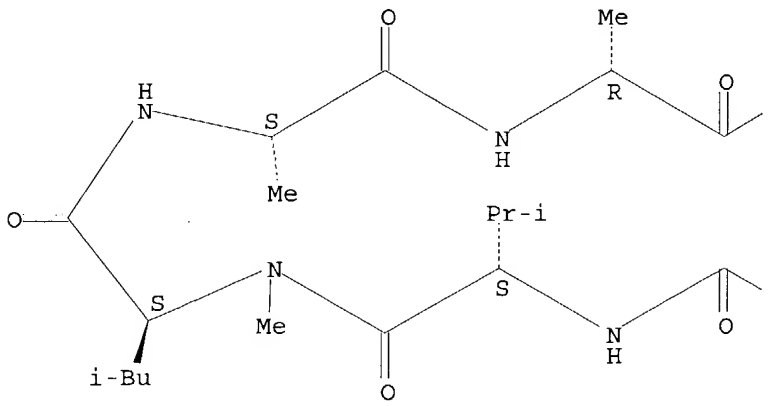
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a polypeptide and an active agent)

IT **59865-13-3**, Cyclosporin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a polypeptide and an active agent)

RN 59865-13-3 HCAPLUS
CN Cyclosporin A (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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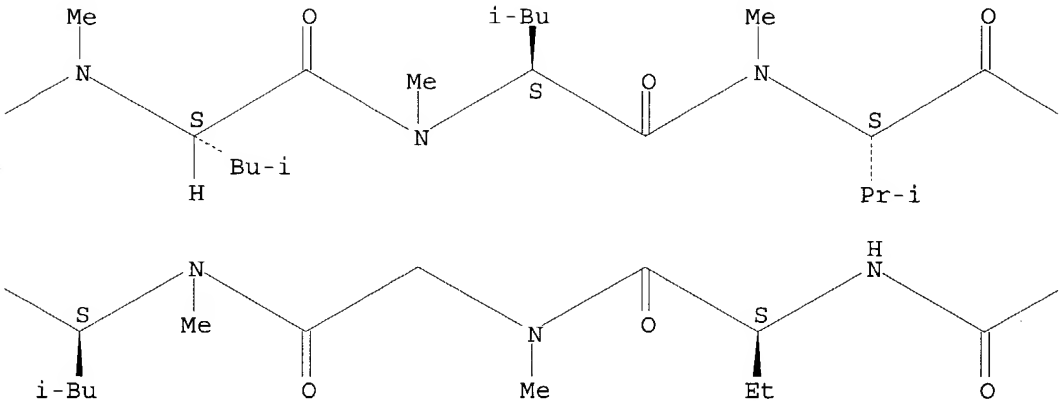
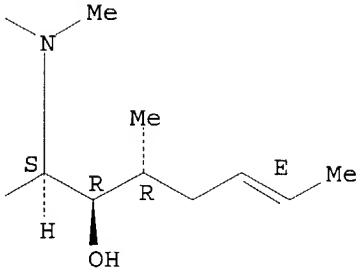


PAGE 1-C



IT **59865-13-3**, Cyclosporin **103475-41-8**, Tepoxalin
121584-18-7, Valspodar **141579-67-1**, A 78773
162011-90-7, Rofecoxib **181695-72-7**, Valdecoxib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a polypeptide and an active agent)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L199 ANSWER 14 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:140525 HCAPLUS
DOCUMENT NUMBER: 138:378518
TITLE: Evaluation of human intestinal absorption data and subsequent derivation of a quantitative structure-activity relationship (QSAR) with the Abraham descriptors. [Erratum to document cited in CA135:266632]
AUTHOR(S): Zhao, Yuan H.; Le, Joelle; Abraham, Michael H.; Hersey, Anne; Eddershaw, Peter J.; Luscombe, Chris N.; Butina, Darko; Beck, Gordon; Sherborne, Brad; Cooper, Ian; Platts, James A.
CORPORATE SOURCE: Department of Chemistry, University College London,

London, WC1H 0AJ, UK
SOURCE: Journal of Pharmaceutical Sciences (2002), 91(2), 605
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The name of author Darko Butina was misspelled as Boutina. This article has recently been awarded the Ebert Prize, given by the APhA for the best paper published in J. Pharm. Sci. in the previous year. The Ebert Prize, one of the top prizes given by the APhA each year, dates approx. from the year 1870.

CC 1-3 (Pharmacology)

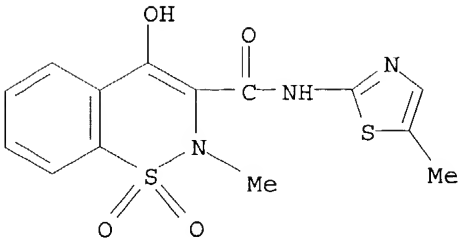
IT 50-02-2, Dexamethasone 50-22-6, Corticosterone 50-23-7, Hydrocortisone 50-24-8, Prednisolone 50-47-5, Desipramine 50-49-7, Imipramine 50-78-2, Acetylsalicylic acid 50-81-7, Ascorbic acid, biological studies 51-34-3, Scopolamine 51-52-5, Propylthiouracil 51-55-8, Atropine 52-01-7, Spironolactone 52-53-9, Verapamil 53-86-1, Indomethacin 54-11-5, Nicotine 54-31-9, Furosemide 54-85-3, Isoniazid 56-40-6, Glycine, biological studies 56-54-2, Quinidine 56-75-7, Chloramphenicol 57-27-2, Morphine, biological studies 57-41-0, Phenytoin 57-63-6, Ethinylestradiol 57-83-0, Progesterone, biological studies 57-92-1, Streptomycin, biological studies 58-08-2, Caffeine, biological studies 58-15-1, Aminopyrine 58-22-0, Testosterone 58-55-9, Theophylline, biological studies 58-93-5, Hydrochlorothiazide 58-94-6, Chlorothiazide 59-05-2, Methotrexate 59-67-6, Nicotinic acid, biological studies 59-92-7, Levodopa, biological studies 60-80-0, Antipyrine 61-33-6, Benzylpenicillin, biological studies 61-75-6, Bretylium tosylate 64-77-7, Tolbutamide 68-41-7, Cycloserine 69-53-4, Ampicillin 69-65-8, Mannitol 69-72-7, Salicylic acid, biological studies 74-55-5, Ethambutol 76-57-3, Codeine 76-99-3, Methadone 81-07-2, Saccharin 81-81-2, Warfarin 83-43-2, Methylprednisolone 87-08-1, Phenoxymethylpenicillin 97-77-8, Disulfiram 99-66-1, Valproic acid 103-90-2, Acetaminophen 104-06-3, Thiacetazone 114-07-8, Erythromycin 125-28-0, Dihydrocodeine 154-21-2, Lincomycin 300-62-9, Amphetamine 427-51-0, Cyproterone acetate 439-14-5, Diazepam 465-65-6, Naloxone 508-77-0, Cymarin 512-69-6, Raffinose 525-66-6, Propranolol 555-30-6, Methyldopa 586-06-1, Metaproterenol 599-79-1, Sulfasalazine 604-75-1, Oxazepam 630-60-4, Ouabain 637-07-0, Clofibrate 657-24-9, Metformin 738-70-5, Trimethoprim 797-63-7, Levonorgestrel 848-75-9, Lormetazepam 1088-11-5, Nordiazepam 1156-05-4, Phenglutarimide 1197-18-8, Tranexamic acid 1225-20-3, Iothalamate sodium 1397-89-3, Amphotericin B 1404-04-2, Neomycin 1812-30-2, Bromazepam 2165-19-7, Guanoxan 2609-46-3, Amiloride 3056-17-5, Stavudine 3375-50-6, Mercaptoethanesulfonic acid 3930-20-9, Sotalol 4205-90-7, Clonidine 4428-95-9, Foscarnet 4618-18-2, Lactulose 5051-62-7, Guanabenz 6452-71-7, Oxprenolol 6673-35-4, Practolol 8063-07-8, Kanamycin 10238-21-8, Glyburide 11003-38-6, Capreomycin 13392-18-2, Fenoterol 13523-86-9, Pindolol 13655-52-2, Alprenolol 15307-86-5, Diclofenac 15421-84-8, Trapidil 15676-16-1, Sulpiride 15686-71-2, Cephalexin 15687-27-1, Ibuprofen 15687-41-9, Oxyfedrine 15722-48-2, Olsalazine 15826-37-6, Cromolyn sodium 15876-67-2, Distigmine bromide 16662-47-8, Gallopamil 17560-51-9, Metolazone 19216-56-9, Prazosin 20448-86-6, Bornaprine 20830-75-5, Digoxin 21187-98-4, Gliclazide 22071-15-4, Ketoprofen 22204-53-1, Naproxen 23031-25-6, Terbutaline 23155-02-4, Fosfomycin 23214-92-8, Doxorubicin 25451-15-4, Felbamate 25614-03-3, Bromocriptine 25876-10-2, Gentamicin-C1 26787-78-0, Amoxicillin 26839-75-8, Timolol 27025-49-6, Carfecillin 27203-92-5, Tramadol 27589-33-9, Azosemide 28395-03-1, Bumetanide 28981-97-7, Alprazolam 29122-68-7, Atenolol 30516-87-1, Zidovudine 31828-71-4, Mexiletine

32953-89-2, Rimiterol 32988-50-4, Viomycin 33279-57-1 33419-42-0, Etoposide 34042-85-8, Sudoxicam 34552-84-6, Isoxicam 34645-84-6, Fenclofenac 34661-75-1, Urapidil 34911-55-2, Bupropion 36104-80-0, Camazepam 36322-90-4, Piroxicam 36791-04-5, Ribavirin 36894-69-6, Labetalol 37517-30-9, Acebutolol 38194-50-2, Sulindac 38304-91-5, Minoxidil 38452-29-8, Tolmesoxide 38677-81-5, Pirbuterol 39562-70-4, Nitrendipine 40505-45-1, AAFC 42200-33-9, Nadolol 46817-91-8, Viloxazine 50370-12-2, Cefadroxil 51384-51-1, Metoprolol 51481-61-9, Cimetidine 51627-14-6, Cefatrizine 51926-52-4, D-Phenylalanyl-L-proline 53583-79-2, Sultopride 54063-54-6, Reproterol 54143-55-4, Flecainide 55268-74-1, Praziquantel 55268-75-2, Cefuroxime 56180-94-0, Acarbose 56187-89-4, Ximoprofen 56211-40-6, Torasemide 59277-89-3, Acyclovir 59804-37-4, Tenoxicam 60142-96-3, Gabapentin 60569-19-9, Propiverine 60607-34-3, Oxatomide 60719-84-8, Amrinone 62571-86-2, Captopril 63590-64-7, Terazosin 63659-18-7, Betaxolol 63675-72-9, Nisoldipine 64544-07-6, Cefuroximeaxetil 65243-33-6, Cefetamet pivoxil 66357-35-5, Ranitidine 66508-37-0, Fosmidomycin 68401-81-0, Ceftizoxime 68506-86-5, Vigabatrin 70052-12-9, Eflornithine 70374-39-9, Lornoxicam 70458-92-3, Pefloxacin 70458-96-7, Norfloxacin **71125-38-7**, Meloxicam 72509-76-3, Felodipine 73384-59-5, Ceftriaxone 73590-58-6, Omeprazole 74103-06-3, Ketorolac 74738-24-2, Recainam 75330-75-5, Lovastatin 75438-57-2, Moxonidine 75695-93-1, Isradipine 75847-73-3, Enalapril 75949-61-0, Pafenolol 76420-72-9, Enalaprilat 76470-66-1, Loracarbef 76541-72-5, Mifobate 76547-98-3, Lisinopril 76824-35-6, Famotidine 76963-41-2, Nizatidine 77181-69-2, Sorivudine 78110-38-0, Aztreonam 78755-81-4, Flumazenil **79217-60-0**, Cyclosporin 81093-37-0, Pravastatin 81098-60-4, Cisapride 81801-12-9, Xamoterol 82410-32-0, Ganciclovir 82419-36-1, Ofloxacin 83366-66-9, Nefazodone 83905-01-5, Azithromycin 84057-84-1, Lamotrigine 84490-12-0, Piroximone 84558-93-0, Netivudine 85721-33-1, Ciprofloxacin 86386-73-4, Fluconazole 86541-75-5, Benazepril 87848-99-5, Acrivastine 89778-26-7, Toremifene 93413-69-5, Venlafaxine 93957-54-1, Fluvastatin 94079-80-8, Cicaprost 97240-79-4, Topiramate 98048-97-6, Fosinopril 99614-02-5, Ondansetron 103577-45-3, Lansoprazole 103628-46-2, Sumatriptan 104227-87-4, Famciclovir 106941-25-7, Adefovir 109889-09-0, Granisetron 113852-37-2, Cidofovir 115103-54-3, Tiagabine 116644-53-2, Mibefradil **120210-48-2**, Tenidap
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of human intestinal drug absorption data and subsequent derivation of QSAR with Abraham descriptors (Erratum))

IT **71125-38-7**, Meloxicam
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of human intestinal drug absorption data and subsequent derivation of QSAR with Abraham descriptors (Erratum))

RN 71125-38-7 HCAPLUS

CN 2H-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-, 1,1-dioxide (9CI) (CA INDEX NAME)



IT **71125-38-7**, Meloxicam **79217-60-0**, Cyclosporin
120210-48-2, Tenidap
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of human intestinal drug absorption data and subsequent derivation of QSAR with Abraham descriptors (Erratum))

L199 ANSWER 15 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:453996 HCAPLUS
DOCUMENT NUMBER: 135:266632
TITLE: Evaluation of human intestinal absorption data and subsequent derivation of a quantitative structure-activity relationship (QSAR) with the Abraham descriptors
AUTHOR(S): Zhao, Yuan H.; Le, Joelle; Abraham, Michael H.; Hersey, Anne; Eddershaw, Peter J.; Luscombe, Chris N.; Boutina, Darko; Beck, Gordon; Sherborne, Brad; Cooper, Ian; Platts, James A.
CORPORATE SOURCE: Department of Chemistry, University College London, London, WC1H 0AJ, UK
SOURCE: Journal of Pharmaceutical Sciences (2001), 90(6), 749-784
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The human intestinal absorption of 241 drugs was evaluated. Three main methods were used to determine the human intestinal absorption: bioavailability, percentage of urinary excretion of drug-related material following oral administration, and the ratio of cumulative urinary excretion of drug-related material following oral and i.v. administration. The general solvation equation developed by Abraham's group was used to model the human intestinal absorption data of 169 drugs we considered to have reliable data. The model contains five Abraham descriptors calculated by the ABSOLV program. The results show that Abraham descriptors can successfully predict human intestinal absorption if the human absorption data is carefully classified based on solubility and administration dose to humans.

CC 1-3 (Pharmacology)
IT 50-02-2, Dexamethasone 50-22-6, Corticosterone 50-23-7, Hydrocortisone 50-24-8, Prednisolone 50-47-5, Desipramine 50-49-7, Imipramine 50-78-2, Acetylsalicylic acid 50-81-7, Ascorbic acid, biological studies 51-34-3, Scopolamine 51-52-5, Propylthiouracil 51-55-8, Atropine, biological studies 52-01-7, Spironolactone 52-53-9, Verapamil 53-86-1, Indomethacin 54-11-5, Nicotine 54-31-9, Furosemide 54-85-3, Isoniazid 56-40-6, Glycine, biological studies 56-54-2, Quinidine 56-75-7, Chloramphenicol 57-27-2, Morphine, biological studies 57-41-0, Phenytoin 57-63-6, Ethinylestradiol 57-83-0, Progesterone,

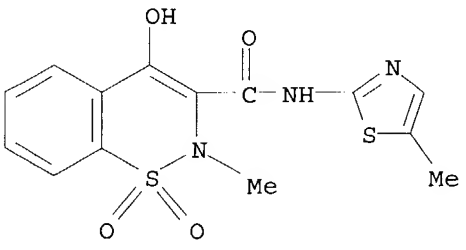
biological studies 57-92-1, Streptomycin, biological studies 58-08-2, Caffeine, biological studies 58-15-1, Aminopyrine 58-22-0, Testosterone 58-55-9, Theophylline, biological studies 58-93-5, Hydrochlorothiazide 58-94-6, Chlorothiazide 59-05-2, Methotrexate 59-67-6, Nicotinic acid, biological studies 59-92-7, Levodopa, biological studies 60-80-0, Antipyrine 61-33-6, Benzylpenicillin, biological studies 61-75-6, Bretylium tosylate 64-77-7, Tolbutamide 68-41-7, Cycloserine 69-53-4, Ampicillin 69-65-8, Mannitol 69-72-7, Salicylic acid, biological studies 74-55-5, Ethambutol 76-57-3, Codeine 76-99-3, Methadone 81-07-2, Saccharin 81-81-2, Warfarin 83-43-2, Methylprednisolone 87-08-1, Phenoxymethylpenicillin 97-77-8, Disulfiram 99-66-1, Valproic acid 103-90-2, Acetaminophen 104-06-3, Thiacetazone 114-07-8, Erythromycin 125-28-0, Dihydrocodeine 154-21-2, Lincomycin 300-62-9, Amphetamine 427-51-0, Cyproterone acetate 439-14-5, Diazepam 465-65-6, Naloxone 508-77-0, Cymarin 512-69-6, Raffinose 525-66-6, Propranolol 555-30-6, Methyldopa 586-06-1, Metaproterenol 599-79-1, Sulfasalazine 604-75-1, Oxazepam 630-60-4, Ouabain 637-07-0, Clofibrate 657-24-9, Metformin 738-70-5, Trimethoprim 797-63-7, Levonorgestrel 848-75-9, Lormetazepam 1088-11-5, Nordiazepam 1156-05-4, Phenglutarimide 1197-18-8, Tranexamic acid 1225-20-3, Iothalamate sodium 1397-89-3, Amphotericin B 1404-04-2, Neomycin 1812-30-2, Bromazepam 2165-19-7, Guanoxan 2609-46-3, Amiloride 3056-17-5, Stavudine 3375-50-6, Mercaptoethanesulfonic acid 3930-20-9, Sotalol 4205-90-7, Clonidine 4428-95-9, Foscarnet 4618-18-2, Lactulose 5051-62-7, Guanabenz 6452-71-7, Oxprenolol 6673-35-4, Practolol 8063-07-8, Kanamycin 10238-21-8, Glyburide 11003-38-6, Capreomycin 13392-18-2, Fenoterol 13523-86-9, Pindolol 13655-52-2, Alprenolol 15307-86-5, Diclofenac 15421-84-8, Trapidil 15676-16-1, Sulpiride 15686-71-2, Cephalexin 15687-27-1, Ibuprofen 15687-41-9, Oxyfedrine 15722-48-2, Olsalazine 15826-37-6, Cromolyn sodium 15876-67-2, Distigmine bromide 16662-47-8, Gallopamil 17560-51-9, Metolazone 19216-56-9, Prazosin 20448-86-6, Bornaprine 20830-75-5, Digoxin 21187-98-4, Gliclazide 22071-15-4, Ketoprofen 22204-53-1, Naproxen 23031-25-6, Terbutaline 23155-02-4, Fosfomycin 23214-92-8, Doxorubicin 25451-15-4, Felbamate 25614-03-3, Bromocriptine 25876-10-2, Gentamicin-C1 26787-78-0, Amoxicillin 26839-75-8, Timolol 27025-49-6, Carfecillin 27203-92-5, Tramadol 27589-33-9, Azosemide 28395-03-1, Bumetanide 28981-97-7, Alprazolam 29122-68-7, Atenolol 30516-87-1, Zidovudine 31828-71-4, Mexiletine 32953-89-2, Rimiterol 32988-50-4, Viomycin 33279-57-1 33419-42-0, Etoposide 34042-85-8, Sudoxicam 34552-84-6, Isoxicam 34645-84-6, Fenclofenac 34661-75-1, Urapidil 34911-55-2, Bupropion 36104-80-0, Camazepam 36322-90-4, Piroxicam 36791-04-5, Ribavirin 36894-69-6, Labetalol 37517-30-9, Acebutolol 37717-21-8, AAFC 38194-50-2, Sulindac 38304-91-5, Minoxidil 38452-29-8, Tolmesoxide 38677-81-5, Pirbuterol 39562-70-4, Nitrendipine 42200-33-9, Nadolol 46817-91-8, Viloxazine 50370-12-2, Cefadroxil 51384-51-1, Metoprolol 51481-61-9, Cimetidine 51627-14-6, Cefatrizine 51926-52-4, D-Phenylalanyl-L-proline 53583-79-2, Sultopride 54063-54-6, Reproterol 54143-55-4, Flecainide 55268-74-1, Praziquantel 55268-75-2, Cefuroxime 56180-94-0, Acarbose 56187-89-4, Ximoprofen 56211-40-6, Torasemide 59277-89-3, Acyclovir 59804-37-4, Tenoxicam 60142-96-3, Gabapentin 60569-19-9, Propiverine 60607-34-3, Oxatomide 60719-84-8, Amrinone 62571-86-2, Captopril 63590-64-7, Terazosin 63659-18-7, Betaxolol 63675-72-9, Nisoldipine 64544-07-6, Cefuroximeaxetil 65243-33-6, Cefetamet pivoxil 66357-35-5, Ranitidine 66508-37-0, Fosmidomycin 68401-81-0, Ceftizoxime 68506-86-5, Vigabatrin 70052-12-9, Eflornithine 70374-39-9, Lornoxicam 70458-92-3, Pefloxacin 70458-96-7, Norfloxacin **71125-38-7**, Meloxicam 72509-76-3, Felodipine 73384-59-5, Ceftriaxone 73590-58-6, Omeprazole

74103-06-3, Ketorolac 74738-24-2, Recainam 75330-75-5, Lovastatin
75438-57-2, Moxonidine 75695-93-1, Isradipine 75847-73-3, Enalapril
75949-61-0, Pafenolol 76420-72-9, Enalaprilat 76470-66-1, Loracarbef
76541-72-5, Mifobate 76547-98-3, Lisinopril 76824-35-6, Famotidine
76963-41-2, Nizatidine 77181-69-2, Sorivudine 78110-38-0, Aztreonam
78755-81-4, Flumazenil **79217-60-0**, Cyclosporin 81093-37-0,
Pravastatin 81098-60-4, Cisapride 81801-12-9, Xamoterol 82410-32-0,
Ganciclovir 82419-36-1, Ofloxacin 83366-66-9, Nefazodone 83905-01-5,
Azithromycin 84057-84-1, Lamotrigine 84490-12-0, Piroximone
84558-93-0, Netivudine 85721-33-1, Ciprofloxacin 86386-73-4,
Fluconazole 86541-75-5, Benazepril 87848-99-5, Acrivastine
89778-26-7, Toremifene 93413-69-5, Venlafaxine 93957-54-1, Fluvastatin
94079-80-8, Cicaprost 97240-79-4, Topiramate 98048-97-6, Fosinopril
99614-02-5, Ondansetron 103577-45-3, Lansoprazole 103628-46-2,
Sumatriptan 104227-87-4, Famciclovir 106941-25-7, Adefovir
109889-09-0, Granisetron 113852-37-2, Cidofovir 115103-54-3, Tiagabine
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(evaluation of human intestinal drug absorption data and subsequent derivation of QSAR with the Abraham descriptors)

IT 116644-53-2, Mibefradil **120210-48-2**, Tenidap 134678-17-4,
Lamivudine 144701-48-4, Telmisartan 146939-27-7, Ziprasidone
147059-75-4, CP99219
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(evaluation of human intestinal drug absorption data and subsequent derivation of QSAR with the Abraham descriptors)

IT **71125-38-7**, Meloxicam
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(evaluation of human intestinal drug absorption data and subsequent derivation of QSAR with the Abraham descriptors)

RN 71125-38-7 HCAPLUS
CN 2H-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-, 1,1-dioxide (9CI) (CA INDEX NAME)



IT **71125-38-7**, Meloxicam **79217-60-0**, Cyclosporin
120210-48-2, Tenidap
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(evaluation of human intestinal drug absorption data and subsequent derivation of QSAR with the Abraham descriptors)

REFERENCE COUNT: 270 THERE ARE 270 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L199 ANSWER 16 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:396644 HCAPLUS
DOCUMENT NUMBER: 135:24671
TITLE: Solid carriers for improved delivery of active ingredients in pharmaceutical compositions
INVENTOR(S): Patel, Manesh V.; Chen, Feng-jing
PATENT ASSIGNEE(S): Lipocine, Inc., USA
SOURCE: PCT Int. Appl., 107 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001037808	A1	20010531	WO 2000-US32255	20001122
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6248363	B1	20010619	US 1999-447690	19991123
EP 1233756	A1	20020828	EP 2000-980761	20001122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003517470	T2	20030527	JP 2001-539423	20001122

PRIORITY APPLN. INFO.: US 1999-447690 A 19991123
WO 2000-US32255 W 20001122

AB The present invention provides solid pharmaceutical compns. for improved delivery of a wide variety of pharmaceutical active ingredients contained therein or sep. administered. In one embodiment, the solid pharmaceutical composition includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. The encapsulation coat can include different combinations of pharmaceutical active ingredients, hydrophilic surfactant, lipophilic surfactants and triglycerides. In another embodiment, the solid pharmaceutical composition includes a solid carrier, the solid carrier being formed of different combinations of pharmaceutical active ingredients, hydrophilic surfactants, lipophilic surfactants and triglycerides. The compns. of the present invention can be used for improved delivery of hydrophilic or hydrophobic pharmaceutical active ingredients, such as drugs, nutritionals, cosmeceuticals and diagnostic agents. A composition contained glyburide 1, PEG 40 stearate 33, glycerol monolaurate 17, and nonpareil seed 80 g.

IC ICM A61K009-14
ICS A61K009-16; A61K009-20; A61K009-46; A61K009-48; A61K009-50; A61K009-54

CC 63-6 (Pharmaceuticals)

IT 50-14-6, Ergocalciferol 50-24-8, Prednisolone 50-28-2, Estradiol, biological studies 50-34-0, Propantheline bromide 50-56-6, Oxytocin, biological studies 51-15-0, Pralidoxime chloride 51-43-4, Epinephrine 51-48-9, L-Thyroxine, biological studies 51-55-8, Atropine, biological studies 51-60-5, Neostigminemethyl sulfate 52-01-7, Spironolactone 52-24-4, Thiotepa 53-43-0, Dehydroepiandrosterone 55-98-1, Busulphan

57-13-6, Urea, biological studies 57-22-7, Vincristine 57-64-7, Physostigmine salicylate 57-83-0, Progesterone, biological studies 57-94-3, Tubocurarine chloride 59-05-2, Methotrexate 60-31-1, Acetylcholine chloride 62-31-7, Dopamine hydrochloride 63-91-2, L-Phenylalanine, biological studies 65-28-1, Phentolamine mesylate 66-76-2, Dicoumarol 67-20-9, Nitrofurantoin 67-45-8, Furazolidone 67-96-9, Dihydrotachysterol 67-97-0, Cholecalciferol 68-19-9, Vitamin b12 69-65-8, D-Mannitol 70-51-9, Deferoxamine 71-27-2, Suxamethonium chloride 74-89-5, Methanamine, biological studies 76-57-3, Codeine 76-90-4, Mepenzolate bromide 76-99-3, Methadone 77-19-0, Dicyclomine 87-33-2, Isosorbide dinitrate 89-57-6, Mesalamine 90-82-4, Pseudoephedrine 101-26-8, Pyridostigmine bromide 104-31-4, Benzonatate 113-15-5, Ergotamine 113-92-8, Chlorpheniramine 114-07-8, Erythromycin 114-80-7, Neostigmine bromide 125-84-8, Aminoglutethimide 126-07-8, Griseofulvin 127-40-2, Lutein 129-06-6, Warfarin sodium 131-49-7, Diatrizoate meglumine 140-64-7, Pentamidine isethionate 147-94-4, Cytarabine 154-21-2, Lincomycin 155-97-5, Pyridostigmine 298-46-4, Carbamazepine 298-57-7, Cinnarizine 298-81-7, Methoxsalen 299-42-3, Ephedrine 300-62-9, Amphetamine 302-79-4, Tretinoin 303-49-1, Clomipramine 303-53-7, Cyclobenzaprine 303-98-0, Coenzyme Q10 321-64-2, Tacrine 359-83-1, Pentazocine 378-44-9, Betamethasone 404-86-4, Capsaicin 437-38-7, Fentanyl 443-48-1, Metronidazole 502-65-8, Lycopene 511-12-6, Dihydroergotamine 520-85-4, Medroxyprogesteron 577-11-7, Sodium docusate 595-33-5 596-51-0, Glycopyrrolate 616-91-1, Acetylcysteine 665-66-7, Amantadine hydrochloride 737-31-5, Diatrizoate sodium 865-21-4, Vinblastine 911-45-5, Clomiphene 1115-70-4, Metformin hydrochloride 1134-47-0, Baclofen 1264-72-8, Colistin sulfate 1319-82-0, Aminocaproic acid 1397-89-3, Amphotericin b 1403-66-3, Gentamycin 1404-90-6, Vancomycin 1405-20-5, Polymyxin B sulfate 1405-37-4, Capreomycin sulfate 1405-87-4, Bacitracin 1406-16-2, Vitamin D 1406-18-4, Vitamin E 1492-18-8, Leucovorin calcium 1501-84-4, Rimantadine hydrochloride 1684-40-8, Tacrine hydrochloride 1695-77-8, Spectinomycin 1951-25-3, Amiodarone 1972-08-3, Tetrahydrocannabinol 2016-88-8, Amiloride hydrochloride 3056-17-5, Stavudine 3485-62-9, Clidinium bromide 3778-73-2, Isofosfamide 3930-20-9, Sotalol 4291-63-8, Cladribine 4419-39-0, Beclomethasone 4759-48-2, Isotretinoin 5104-49-4, Flurbiprofen 5534-95-2, Pentagastrin 6493-05-6, Pentoxifylline 7261-97-4, Dantrolene 7414-83-7, Disodium etidronate 7481-89-2, Zalcitabine 7648-98-8, Ambenonium 7689-03-4, Camptothecin 8068-28-8, Colistimethate sodium 9001-27-8, Factor VIII 9001-28-9, Factor IX 9002-01-1, Streptokinase 9002-60-2, Corticotropin, biological studies 9002-61-3, Chorionic gonadotropin 9004-17-5, NPH insulin 9004-99-3, Polyethylene glycol stearate 9005-63-4D, Polyoxyethylene sorbitan, fatty acid esters 9007-92-5, Glucagon, biological studies 9015-68-3, Asparaginase 9034-40-6, Gonadotropin-releasing hormone 9039-53-6, Urokinase 9041-08-1, Dalteparin sodium 9041-93-4, Bleomycin sulfate 9087-70-1, Aprotinin 10238-21-8, Glibenclamide 10540-29-1, Tamoxifen 10596-23-3, Clodronic acid 11000-17-2, Vasopressin 11061-68-0, Insulin (human) 11103-57-4, Vitamin A 12001-79-5, Vitamin K 12584-58-6, Porcine insulin 13265-10-6, Methscopolamine 15307-86-5, Diclofenac 15500-66-0, Pancuronium bromide 15574-96-6, Pizotifen 15663-27-1, Cisplatin 15686-51-8, Clemastine 15686-71-2, Cephalexin 15687-27-1, Ibuprofen 15826-37-6, Cromolyn sodium 16679-58-6, Desmopressin 16960-16-0, Cosyntropin 17230-88-5, Danazol 18323-44-9, Clindamycin 18559-94-9, Albuterol 18883-66-4, Streptozocin 19356-17-3, Calcifediol 20537-88-6, Amifostine 20594-83-6, Nalbuphine 20830-75-5, Digoxin 21215-62-3, Human calcitonin 21256-18-8, Oxaprozin 21679-14-1, Fludarabine 21829-25-4, Nifedipine 22254-24-6, Ipratropium bromide 22916-47-8, Miconazole 23031-32-5, Terbutaline sulfate 23214-92-8,

Doxorubicin 23288-49-5, Probucol 24356-60-3, Cephapirin sodium 25126-32-3, Sincalide 25322-68-3D, PEG, esters 25523-97-1, Dexchlorpheniramine 25618-55-7D, Polyglycerol, fatty acid esters 25812-30-0, Gemfibrozil 26839-75-8, Timolol 27164-46-1, Cefazolin sodium 27203-92-5, Tramadol 27215-38-9, Glycerol monolaurate 29094-61-9, Glipizide 29122-68-7, Atenolol 29767-20-2, Teniposide 30516-87-1, Zidovudine 32222-06-3, Calcitriol 33069-62-4, Paclitaxel 33419-42-0, Etoposide 33515-09-2, Gonadorelin 33564-30-6, Cefoxitin sodium 34787-01-4, Ticarcillin 34911-55-2, Bupropion 35607-66-0, Cefoxitin 36791-04-5, Ribavirin 38304-91-5, Minoxidil 41340-25-4, Etodolac 41575-94-4, Carboplatin 42057-22-7, Mezlocillin sodium 42540-40-9, Cefamandole nafate 42924-53-8, Nabumetone 43200-80-2, Zopiclone 47931-85-1, Salmon calcitonin 49562-28-9, Fenofibrate 49697-38-3, Rimexolone 50700-72-6, Vecuronium bromide 51110-01-1, Somatostatin 51322-75-9, Tizanidine 51333-22-3, Budesonide 51384-51-1, Metoprolol 51481-61-9, Cimetidine 53123-88-9, Sirolimus 53179-11-6, Loperamide 53230-10-7, Mefloquine 53910-25-1, Pentostatin 54063-53-5, Propafenone 54910-89-3, Fluoxetine 54965-21-8, Albendazole 55142-85-3, Ticlopidine 56180-94-0, Acarbose 57248-88-1, Pamidronate disodium 59277-89-3, Acyclovir 59467-70-8, Midazolam 59703-84-3, Piperacillin sodium **59865-13-3**, Cyclosporine 60142-96-3, Neurontin 61270-78-8, Cefonicid sodium 61379-65-5, Rifapentine 61869-08-7, Paroxetine 62013-04-1, Dirithromycin 62893-19-0, Cefoperazone 63585-09-1, Foscarnet sodium 63612-50-0, Nilutamide 63675-72-9, Nisoldipine 64228-81-5, Atracurium besylate 64544-07-6, Cefuroxime axetil 65271-80-9, Mitoxantrone 65277-42-1, Ketoconazole 66376-36-1, Alendronate 68099-86-5, Bepridil hydrochloride 68401-81-0, Ceftizoxime 68506-86-5, Vigabatrin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(solid carriers for improved delivery of active ingredients in pharmaceutical compns.)

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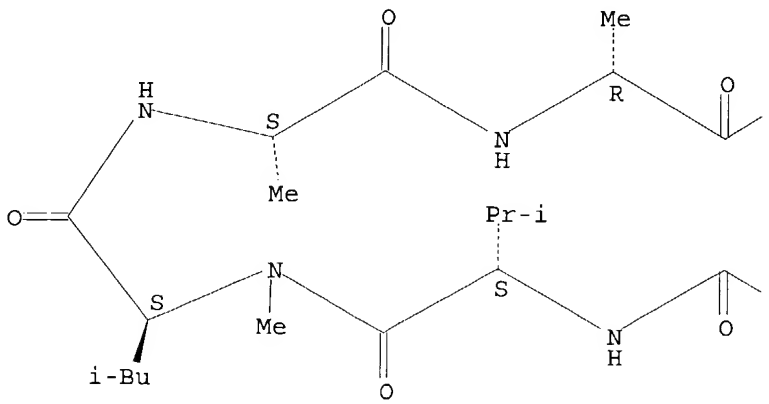
106392-12-5, Oxirane, polymer with methyloxirane, block 106650-56-0, Sibutramine 106819-53-8, Doxacurium chloride 106861-44-3, Mivacurium chloride 107648-80-6, Cefepime hydrochloride 107753-78-6, Zafirlukast 109319-16-6, Factor VIII 110871-86-8, Sparfloxacin 111025-46-8, Pioglitazone **111406-87-2**, Zileuton 112965-21-6, Calcipotriene 113427-24-0 113665-84-2, Clopidogrel 113852-37-2, Cidofovir 115103-54-3, Tiagabine 116094-23-6, Insulin aspart 117976-89-3, Rabeprazole 118072-93-8, Zoledronate 118292-40-3, Tazarotene 119914-60-2, Grepafloxacin 120014-06-4, Donepezil 121368-58-9, Olpadronate 121679-13-8, Naratriptan 122320-73-4, Rosiglitazone 123948-87-8, Topotecan 124832-26-4, Valaciclovir 127759-89-1, Lobucavir 127779-20-8, Saquinavir 129497-78-5, Verteporfin 131918-61-1, Paricalcitol 133040-01-4, Eprosartan 133107-64-9, Insulin lispro 134523-00-5, Atorvastatin 134678-17-4, Lamivudine 135062-02-1, Repaglinide 137862-53-4, Valsartan 138402-11-6, Irbesartan 139110-80-8, Zanamivir 139264-17-8, Zolmitriptan 139481-59-7, Candesartan 139639-23-9, Tissue type plasminogen activator 142128-59-4, Terzolin 143003-46-7, Alglucerase 143011-72-7, Granulocyte colony stimulating factor 143831-71-4 144034-80-0, Rizatriptan 144494-65-5, Tirofiban 144701-48-4, Telmisartan 145599-86-6, Cerivastatin 145941-26-0, Oprelvekin 146961-76-4, Alatrofloxacin 147059-72-1, Trovafloxacin 148553-50-8, Pregabalin 151126-32-8, Pramlintide 153559-49-0, Targretin 154361-50-9, Capecitabine 154598-52-4, Efavirenz 155213-67-5, Ritonavir 157810-81-6, Indinavir sulfate 158747-02-5, Frovatriptan 158966-92-8, Montelukast 159989-64-7, Nelfinavir 160337-95-1, Insulin glargine **162011-90-7**, Rofecoxib 165101-51-9, Becaplermin 169148-63-4, Insulin detemir 169590-42-5, Celecoxib 171599-83-0, Sildenafil citrate 173146-27-5, Denileukin diftitox 191588-94-0, TNK-tPA
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(solid carriers for improved delivery of active ingredients in pharmaceutical compns.)

IT **59865-13-3**, Cyclosporine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(solid carriers for improved delivery of active ingredients in pharmaceutical compns.)

RN 59865-13-3 HCAPLUS
CN Cyclosporin A (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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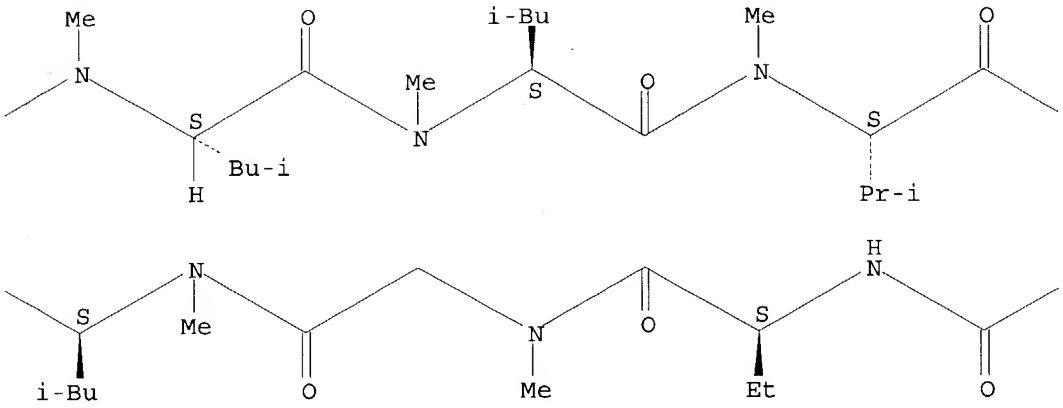

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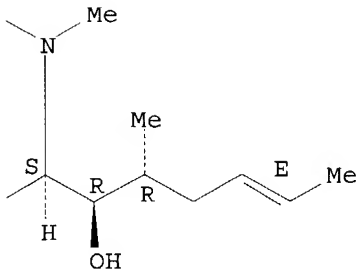


IT **59865-13-3**, Cyclosporine **111406-87-2**, Zileuton
162011-90-7, Rofecoxib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(solid carriers for improved delivery of active ingredients in pharmaceutical compns.)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L199 ANSWER 17 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	2001:300514 HCAPLUS
DOCUMENT NUMBER:	134:331617
TITLE:	Oil-in-water emulsion compositions for polyfunctional active ingredients
INVENTOR(S):	Chen, Feng-jing; Patel, Mahesh V.
PATENT ASSIGNEE(S):	Lipocine, Inc., USA
SOURCE:	PCT Int. Appl., 82 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001028555	A1	20010426	WO 2000-US28835	20001018
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002107265	A1	20020808	US 1999-420159	19991018
US 6720001	B2	20040413		

PRIORITY APPLN. INFO.: US 1999-420159 A 19991018

AB Pharmaceutical oil-in-water emulsions for delivery of polyfunctional active ingredients with improved loading capacity, enhanced stability, and reduced irritation and local toxicity are described. Emulsions include an aqueous phase, an oil phase comprising a structured triglyceride, and an emulsifier. The structured triglyceride of the oil phase is substantially free of triglycerides having three medium chain (C6-C12) fatty acid moieties, or a combination of a long chain triglyceride and a polarity-enhancing polarity modifier. The present invention also provides methods of treating an animal with a polyfunctional active ingredient, using dosage forms of the pharmaceutical emulsions. For example, an emulsion was prepared, with cyclosporin A as the polyfunctional active ingredient dissolved in an oil phase including a structured triglyceride (Captex 810D) and a long chain triglyceride (safflower oil). The composition contained (by weight) cyclosporin A 1.0, Captex 810D 5.0, safflower oil 5.0, BHT 0.02, egg phospholipid 2.4, dimyristoylphosphatidyl glycerol 0.2, glycerol 2.25, EDTA 0.01, and water up to 100%, resp.

IC ICM A61K031-355
ICS A61K031-20

CC 63-6 (Pharmaceuticals)

IT 50-14-6, Ergocalciferol 50-21-5D, Lactic acid, glycerides 50-24-8, Prednisolone 50-28-2, Estradiol, biological studies 50-34-0, Propantheline bromide 50-56-6, Oxytocin, biological studies 50-70-4, Sorbitol, biological studies 51-15-0, Pralidoxime chloride 51-43-4, Epinephrine 51-48-9, L-Thyroxine, biological studies 51-55-8, Atropine, biological studies 51-60-5, Neostigmine methyl sulfate 52-01-7, Spironolactone 52-24-4, Thiotepa 55-98-1, Busulfan 56-81-5, Glycerol, biological studies 57-13-6, Urea, biological studies 57-22-7, Vincristine 57-55-6, Propylene glycol, biological studies 57-55-6D, Propylene glycol, fatty acid esters 57-64-7, Physostigmine salicylate 57-83-0, Progesterone, biological studies 57-88-5, Cholesterol, biological studies 57-88-5D, Cholesterol, fatty acid esters and polyethoxylated 57-94-3, Tubocurarine chloride 59-05-2, Methotrexate 60-31-1, Acetylcholine chloride 62-31-7, Dopamine hydrochloride 63-91-2, Phenylalanine, biological studies 64-17-5, Ethanol, biological studies 65-28-1, Phentolamine mesylate 66-76-2, Dicoumarol 67-20-9, Nitrofurantoin 67-45-8, Furazolidone 67-96-9, Dihydrotachysterol 67-97-0, Cholecalciferol 68-19-9, Vitamin B12 69-65-8, D-Mannitol 70-51-9, Deferoxamine 71-27-2, Suxamethonium chloride 74-89-5, Methanamine, biological studies 76-57-3, Codeine 76-90-4, Mepenzolate bromide 76-99-3, Methadone 77-19-0, Dicyclomine 83-44-3, Deoxycholic acid 87-33-2, Isosorbide dinitrate 89-57-6, Mesalamine 101-26-8, Pyridostigmine bromide 104-31-4, Benzonatate 107-21-1, Ethylene glycol, biological studies 112-80-1, Oleic acid,

biological studies 113-15-5, Ergotamine 113-92-8, Chlorpheniramine 114-07-8, Erythromycin 114-80-7, Neostigmine bromide 115-77-5, Pentaerythritol, biological studies 121-44-8, Triethylamine, biological studies 122-32-7, Glyceryl trioleate 125-84-8, Aminoglutethimide 126-07-8, Griseofulvin 129-06-6, Warfarin sodium 131-49-7, Diatrizoate meglumine 140-64-7, Pentamidine isethionate 147-94-4, Cytarabine 154-21-2, Lincomycin 155-97-5, Pyridostigmine 298-46-4, 5H-Dibenz[b,f]azepine-5-carboxamide 298-57-7, Cinnarizine 298-81-7, Methoxsalen 299-42-3, Ephedrine 300-62-9, Amphetamine 302-79-4, Tretinoin 303-49-1, Clomipramine 321-64-2, Tacrine 359-83-1, Pentazocine 378-44-9, Betamethasone 404-86-4, Capsaicin 437-38-7, Fentanyl 443-48-1, Metronidazole 502-65-8, Lycopene 511-12-6, Dihydroergotamine 520-85-4, Medroxyprogesterone 537-40-6, Glyceryl trilinoleate 541-15-1, Carnitine 595-33-5 596-51-0, Glycopyrrolate 616-91-1, Acetylcysteine 665-66-7, Amantadine hydrochloride 737-31-5, Diatrizoate sodium 865-21-4, Vinblastin 911-45-5, Clomiphene 1115-70-4, Metformin hydrochloride 1134-47-0, Baclofen 1264-72-8, Colistin sulfate 1319-82-0, Aminocaproic acid 1397-89-3, Amphotericin B 1403-66-3, Gentamycin 1404-90-6, Vancomycin 1405-20-5, Polymixin B sulfate 1405-37-4, Capreomycin sulfate 1405-87-4, Bacitracin 1406-16-2, Vitamin D 1406-18-4, Vitamin E 1492-18-8, Leucovorin calcium 1501-84-4, Rimantadine hydrochloride 1684-40-8, Tacrine hydrochloride 1695-77-8, Spectinomycin 1951-25-3, Amiodarone 1972-08-3, Tetrahydrocannabinol 2016-88-8, Amiloride hydrochloride 3056-17-5, Stavudine 3485-62-9, Clidinium bromide 3778-73-2, Isofosfamide 3930-20-9, Sotalol 4291-63-8, Cladribine 4419-39-0, Beclomethasone 4759-48-2, Isotretinoin 5104-49-4, Flurbiprofen 5534-95-2, Pentagastrin 6493-05-6, Pentoxifylline 6990-06-3, Fusidic acid 7261-97-4, Dantrolene 7414-83-7, Etidronate disodium 7481-89-2, Zalcitabine 7648-98-8, Ambenonium 7689-03-4, Camptothecin 8068-28-8, Colistimethate sodium 9001-28-9, Factor IX 9002-01-1, Streptokinase 9002-60-2, Corticotropin, biological studies 9004-17-5, NPH insulin 9005-07-6, PEG 400 dioleate 9005-63-4D, fatty acid esters 9007-48-1, Plurol Oleique CC497 9007-92-5, Glucagon, biological studies 9015-68-3, Asparaginase 9034-40-6, Gonadotropin releasing hormone 9039-53-6, Urokinase 9041-08-1, Dalteparin sodium 9041-93-4, Bleomycin sulfate 9087-70-1, Aprotinin 10238-21-8, Glyburide 10540-29-1, Tamoxifen 10596-23-3, Clodronic acid 11000-17-2, Vasopressin 11061-68-0, Human insulin 11103-57-4, Vitamin A 11140-04-8, Imwitor 988 12001-79-5, Vitamin K 12584-58-6, Insulin porcine 12619-70-4, Cyclodextrin 12629-01-5, Human growth hormone 13265-10-6, Methscopolamine 14465-68-0, Glyceryl trilinolenate 15307-86-5, Diclofenac 15500-66-0, Pancuronium bromide 15574-96-6, Pizotifen 15663-27-1, Cisplatin 15686-51-8, Clemastine 15686-71-2, Cephalexin 15687-27-1, Ibuprofen 15826-37-6, Cromolyn sodium 16679-58-6, Desmopressin 16960-16-0, Cosyntropin 17230-88-5, Danazol 18323-44-9, Clindamycin 18559-94-9, Albuterol 18883-66-4, Streptozocin 19356-17-3, Calcifediol 20537-88-6, Amifostine 20594-83-6, Nalbuphine 20830-75-5, Digoxin 21215-62-3, Human calcitonin 21256-18-8, Oxaprozin 21679-14-1, Fludarabine 21829-25-4, Nifedipine 22254-24-6, Ipratropium bromide 22916-47-8, Miconazole 23031-32-5, Terbutaline sulfate 23214-92-8, Doxorubicin 23288-49-5, Probucol 24356-60-3, Cephapirin sodium 25126-32-3, Sincalide 25322-68-3, Polyethylene glycol 25322-69-4, Polypropylene glycol 25523-97-1, Dexchlorpheniramine 25618-55-7, Polyglycerol 25812-30-0, Gemfibrozil 26839-75-8, Timolol 27164-46-1, Cefazolin sodium 27203-92-5, Tramadol 29094-61-9, Glipizide 29122-68-7, Atenolol 29767-20-2, Teniposide 30516-87-1, Zidovudine 32222-06-3, Calcitriol 33069-62-4, Paclitaxel 33419-42-0, Etoposide 33515-09-2, Gonadorelin 33564-30-6, Cefoxitin sodium 34787-01-4, Ticarcillin 34911-55-2, Bupropion 36791-04-5, Ribavirin

37220-82-9, Peceol 37321-62-3, Lauroglycol FCC 38304-91-5, Minoxidil
39809-25-1, Penciclovir 41340-25-4, Etodolac 41575-94-4, Carboplatin
42057-22-7, Mezlocillin sodium 42540-40-9, Cefamandole nafate
42924-53-8, Nabumetone 43200-80-2, Zopiclone 47931-85-1, Calcitonin
salmon 49562-28-9, Fenofibrate 49697-38-3, Rimexolone 50700-72-6,
Vecuronium bromide 51110-01-1, Somatostatin 51322-75-9, Tizanidine
51333-22-3, Budesonide 51384-51-1, Metoprolol 51481-61-9, Cimetidine
53123-88-9, Sirolimus 53179-11-6, Loperamide 53230-10-7, Mefloquine
53910-25-1, Pentostatin 54063-53-5, Propafenone 54910-89-3, Fluoxetine
54965-21-8, Albendazole 55079-83-9, Acitretin 55142-85-3, Ticlopidine
56180-94-0, Acarbose 57248-88-1, Pamidronate disodium 59277-89-3,
Acyclovir 59467-70-8, Midazolam 59703-84-3, Piperacillin sodium
59865-13-3, Cyclosporin A
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oil-in-water emulsion compns. for polyfunctional active ingredients)

IT 60142-96-3, Gabapentin 61270-78-8, Cefonicid sodium 61361-72-6,
Dimyristoylphosphatidyl glycerol 61379-65-5, Rifapentine 61489-71-2,
Menotropin 61869-08-7, Paroxetine 62013-04-1, Dirithromycin
62356-64-3 62893-19-0, Cefoperazone 63527-52-6, Cefotaxime
63585-09-1, Foscarnet sodium 63590-64-7, Terazosin 63612-50-0,
Nilutamide 63675-72-9, Nisoldipine 64228-81-5, Atracurium besylate
64544-07-6, Cefuroxime axetil 65271-80-9, Mitoxantrone 65277-42-1,
Ketoconazole 66376-36-1, Alendronate 66419-50-9, Bovine growth hormone
68099-86-5, Bepridil hydrochloride 68401-81-0, Ceftizoxime 68506-86-5,
Vigabatrin 69049-74-7, Nedocromil sodium 69655-05-6, Didanosine
69756-53-2, Halofantrine 70288-86-7, Ivermectin 70458-92-3, Pefloxacin
70458-96-7, Norfloxacin 71486-22-1, Vinorelbine 72432-03-2, Miglitol
72559-06-9, Rifabutine 73384-59-5, Ceftriaxone 73590-58-6, Omeprazole
73963-72-1, Cilostazol 74011-58-8, Enoxacin 74103-06-3, Ketorolac
74356-00-6, Cefotetan disodium 74381-53-6, Leuprolide acetate
75706-12-6, Leflunomide 76420-72-9, Enalaprilat 76470-66-1, Loracarbef
76547-98-3, Lisinopril 76824-35-6, Famotidine 76963-41-2, Nizatidine
78110-38-0, Aztreonam 79350-37-1, Cefixime 79517-01-4, Octreotide
acetate 79617-96-2, Sertraline 79794-75-5, Loratadine 79902-63-9,
Simvastatin 81093-37-0, Pravastatin 81098-60-4, Cisapride
81103-11-9, Clarithromycin 81161-17-3, Esmolol hydrochloride
82410-32-0, Ganciclovir 82419-36-1, Ofloxacin 82626-48-0, Zolpidem
82952-64-5, Trimetrexate glucuronate 83799-24-0, Fexofenadine
83869-56-1, Granulocyte-macrophage colony stimulating factor 83881-51-0,
Cetirizine 83905-01-5, Azithromycin 84057-84-1, Lamotrigine
84371-65-3, Mifepristone 84449-90-1, Raloxifene 84625-61-6,
Itraconazole 85721-33-1, Ciprofloxacin 86386-73-4, Fluconazole
86541-75-5, Benazepril 87679-37-6, Trandolapril 88669-04-9,
Trospectomycin 89778-26-7, Toremifene 89987-06-4, Tiludronate
90357-06-5, Bicalutamide 91161-71-6, Terbinafine 93390-81-9,
Fosphenytoin 93413-69-5, Venlafaxine 93479-97-1, Glimepiride
93957-54-1, Fluvastatin 94749-08-3, Salmeterol xinafoate 95233-18-4,
Atovaquone 97240-79-4, Topiramate 97322-87-7, Troglitazone
97682-44-5, Irinotecan 98079-51-7, Lomefloxacin 98319-26-7,
Finasteride 100986-85-4, Levofloxacin 101828-21-1, Butenafine
103577-45-3, Lansoprazole 103628-46-2, Sumatriptan 104227-87-4,
Famciclovir 104987-11-3, Tacrolimus 105462-24-6, Risedronic acid
106133-20-4, Tamsulosin 106650-56-0, Sibutramine 106819-53-8,
Doxacurium chloride 106861-44-3, Mivacurium chloride 107648-80-6,
Cefepime hydrochloride 107753-78-6, Zafirlukast 110871-86-8,
Sparfloxacin 111025-46-8, Pioglitazone **111406-87-2**, Zileuton
112965-21-6, Calcipotriene 113189-02-9, Antihemophilic factor
113665-84-2, Clopidogrel 113852-37-2, Cidofovir 115103-54-3, Tiagabine
116094-23-6, Insulin aspart 117976-89-3, Rabeprazole 118072-93-8,
Zoledronate 118292-40-3, Tazarotene 119914-60-2, Grepafloxacin

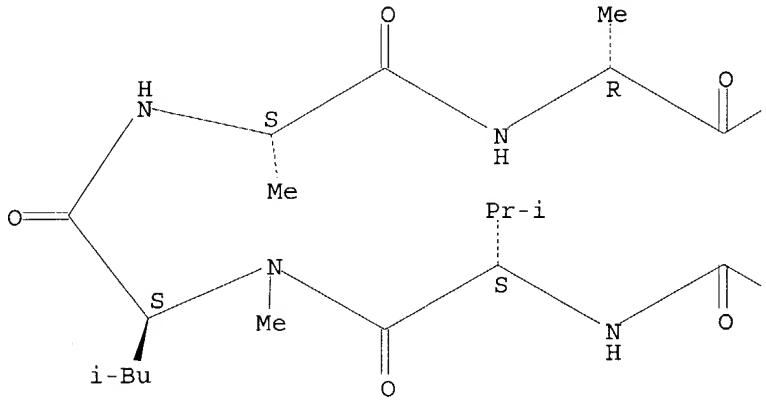
120014-06-4, Donepezil 121368-58-9, Olpadronate 121679-13-8, Naratriptan 122320-73-4, Rosiglitazone 123948-87-8, Topotecan 124832-26-4, Valaciclovir 127759-89-1, Lobucavir 127779-20-8, Saquinavir 129497-78-5, Verteporfin 131918-61-1, Paricalcitol 133040-01-4, Eprosartan 133107-64-9, Insulin lispro 134523-00-5, Atorvastatin 134678-17-4, Lamivudine 135062-02-1, Repaglinide 137862-53-4, Valsartan 138402-11-6, Irbesartan 139110-80-8, Zanamivir 139264-17-8, Zolmitriptan 139481-59-7, Candesartan 139639-23-9, Tissue type plasminogen activator 143003-46-7, Alglucerase 143011-72-7, Granulocyte colony stimulating factor 144034-80-0, Rizatriptan 144494-65-5, Tirofiban 144701-48-4, Telmisartan 145599-86-6, Cerivastatin 145941-26-0, Oprelvekin 146961-76-4, Alatrofloxacin 147059-72-1, Trovafloxacin 148553-50-8, Pregabalin 151126-32-8, Pramlintide 153559-49-0, Targretin 154361-50-9, Capecitabine 154598-52-4, Efavirenz 155213-67-5, Ritonavir 156259-68-6, Capmul MCM 157810-81-6, Indinavir sulfate 158747-02-5, Frovatriptan 158966-92-8, Montelukast 159989-64-7, Nelfinavir 160337-95-1, Insulin glargine **162011-90-7**, Rofecoxib 165101-51-9, Becaplermin 169148-63-4, Insulin detemir 169590-42-5, Celecoxib 173146-27-5, Denileukin diftitox 191588-94-0, TNK-tPA 208666-87-9, Captex 810D
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oil-in-water emulsion compns. for polyfunctional active ingredients)

IT **59865-13-3**, Cyclosporin A
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oil-in-water emulsion compns. for polyfunctional active ingredients)

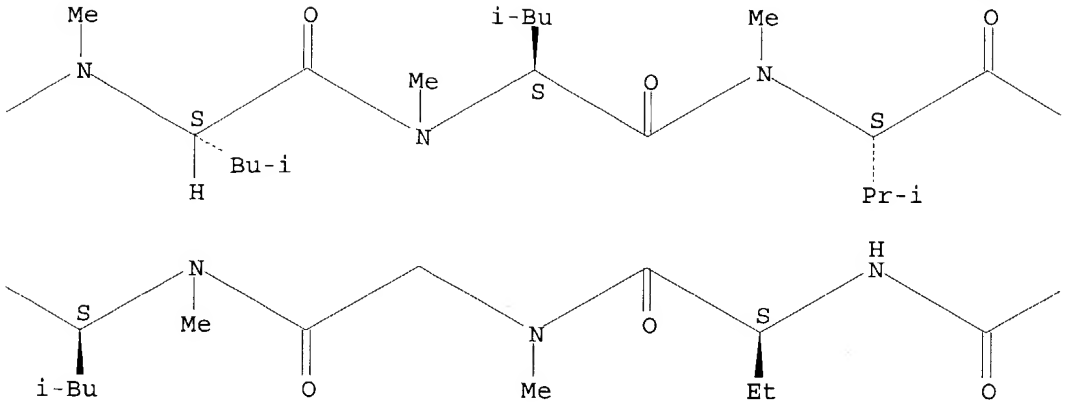
RN 59865-13-3 HCAPLUS
CN Cyclosporin A (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

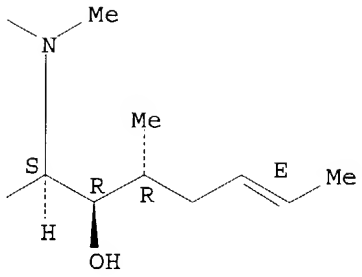
PAGE 1-A



PAGE 1-B



PAGE 1-C



IT **59865-13-3**, Cyclosporin A **111406-87-2**, Zileuton
162011-90-7, Rofecoxib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oil-in-water emulsion compns. for polyfunctional active ingredients)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L199 ANSWER 18 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:754502 HCAPLUS
DOCUMENT NUMBER: 133:321880
TITLE: Treatment of inflammation and inflammation-related disorders with a combination of a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor.
INVENTOR(S): Isakson, Peter C.; Anderson, Gary D.; Gregory, Susan A.
PATENT ASSIGNEE(S): G.D. Searle and Co., USA
SOURCE: U.S. 21 pp. Cont. in-part of U.S. Ser. No. 489,472,

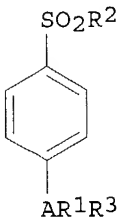
Applicants

DOCUMENT TYPE:
LANGUAGE:
FAMILY ACC. NUM. COUNT

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6136839	A	20001024	US 1996-661660	19960611
CA 2224517	AA	19961227	CA 1996-2224517	19960611

PRIORITY APPLN. INFO.: US 1995-489472 B2 19950612
OTHER SOURCE(S): MARPAT 133:321880
GI



I

AB A combination comprising a 5-lipoxygenase inhibitor and a cyclooxygenase-2 inhibitor selected from title compds. [I; A = pyrazolyl; R1 = ≥1 of (substituted) heterocyclyl, cycloalkyl, cycloalkenyl, aryl; R2 = Me, amino; R3 = H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, CO2H, cyanoalkyl, heterocyclyloxy, alkoxy, alkylthio, alkylcarbonyl, aryl, haloalkyl, etc.], is claimed. Thus, EtO2CCHF2 in MeOCMe3 was treated with NaOMe and then with 3-fluoro-4-methoxyacetophenone (preparation given) followed by 16 h stirring to give 96% 4,4-difluoro-1-(3-fluoro-4-methoxyphenyl)butane-1,3-dione. This was refluxed 16 h with 4-sulfonamidophenylhydrazine hydrochloride in EtOH to give 87% 4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl-1H-pyrazol-1-yl]benzenesulfonamide (II). II with 6-[[3-fluoro-5-(3,4,5,6-tetrahydro-4-methoxy-2H-pyran-4-yl)phenoxy]methyl]-1-methyl-1H-quinazolin-2-one (III) at 30 mpk/day orally in mice in the collagen-induced arthritis screen reduced incidence of arthritis to 20% (vs. 100% for controls). A formulation containing II and III is given.

IC ICM A61K031-415
ICS A61K031-34

NCL 514406000

CC 28-8 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

IT **141579-67-1P 169590-41-4P 170569-86-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(treatment of inflammation and inflammation-related disorders with a combination of a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor)

IT **341-88-8**, KF 8940 **4737-26-2**, Isoflavan
27686-84-6, Masoprocol **34334-69-5**, Cirsiliol
36441-32-4, DuP 654 **46721-85-1**, CBS 1114 50847-11-5,
Ibudilast **60284-71-1**, AHR 5333 **75139-38-7**,
Carbazomycin B **79916-77-1**, Forsythiaside **80809-81-0**,
Docebenone **87660-25-1**, ONO 5349 **91431-42-4**, Lonapalene
92532-05-3, Rev 5367 **93211-49-5**, L 651392
96314-49-7, TEI 8005 **96920-48-8**, TMK 992
96928-53-9, TMK 919 **99107-52-5**, Bunaprolast
99134-29-9, L 651896 **99318-09-9**, QA 208-199

100035-75-4, Evandamine **101335-99-3**, Eprovafen
101618-31-9, TMK 789 **101619-08-3**, TMK 781
101619-11-8, TMK 777 **101910-24-1**, PF 5901
102612-16-8, L 656224 **103141-09-9**, FPL 62064
103475-41-8, Tepoxalin **104007-80-9**, TZI 41127
104153-37-9, Rilopirox **105357-17-3**, SC 41661A
107008-29-7, L 652343 **107746-52-1**, E 5110
107889-32-7, LY 178002 **110033-17-5**, WY 47288
110406-33-2 110501-66-1, TMK 688 **110545-79-4**, SCH
40120 **111406-87-2**, Zileuton **111525-11-2**, A 63162
111908-94-2, SK&F 104351 **111908-95-3**, SK&F 104493
111974-60-8, WY 48252 **112344-52-2**, Flobufen
114832-13-2, CGS 8515 **114917-95-2**, BMY 30094
115255-10-2, ONO-LP 219 **115255-23-7**, ONO-LP 269
115816-05-2, BI-L 93BS **117574-40-0**, CV 6504
118414-82-7, L 663536 **118420-47-6**, AL 3264
119256-94-9, FR 110302 **120164-49-0**, E 6080
120210-48-2, Tenidap **120602-97-3**, RG 6866
121135-51-1 **121412-39-3**, CGS 21595 **121502-05-4**
, PD 127443 **122454-69-7**, SK&F 105809 **122610-85-9**, A
65260 **123016-21-7**, WY 50295 **123606-23-5**, A 69412
125578-25-8 **125721-82-6**, BIL 226XX **125722-16-9**,
Enofelast **127245-22-1**, BF 389 **127378-46-5**, CI 987
127481-38-3, L 674636 **128253-31-6**, Bay-x-1005
129424-08-4, ICI 211965 **130116-16-4**, CI 986
130838-15-2, Y 19432 **131817-86-2**, CGS 22745
132392-65-5, LY 269415 **132734-43-1**, LY 233569
132956-22-0, Enazadrem phosphate **133174-26-2**, L 670630
133430-69-0, ETH 615 **134470-36-3**, BW-B 218C
134470-38-5, BW-B 70C **134822-78-9**, CGS 23885
134823-10-2, CGS 24891 **135133-84-5**, SC 45662
135872-69-4, WAY 120739 **135872-94-5**, WAY 121520
137945-48-3 **138331-04-1**, R 68151 **139149-55-6**, SB
202235 **139340-56-0**, CI 1004 **140841-32-3**
141579-54-6, A 76745 **141579-87-5**, A 79175
143964-80-1, F 1322 **145096-30-6**, E 3040
146935-39-9, Epocarbazolin a **147030-01-1**, MK 591
147317-96-2, Nitrosoxacin A 147432-77-7, Ontazolast
147497-10-7, CGS 26529 **147936-06-9**, L 699333
148915-76-8, BU 4601A **149539-02-6**, BI-L 357
150693-65-5, Lagunamycin 152784-11-7, WILD 20
153950-29-9, A 121798 **154214-70-7**, R 85355
154355-76-7, ABT 761 **155944-23-3**, ZM 230487
156897-06-2, ML 3000 157630-13-2, MER W 8020 **158930-07-5**
, L 739010 161435-44-5, CGS 25997 162738-34-3 169590-42-5
171095-65-1, CMI 568 **187112-03-4**, A 72694 **187112-04-5**,
a 80263 **187112-09-0**, Bay-q-1531 **187112-10-3**, BF 397
187112-11-4, BW 4C **187112-12-5**, BW 70C
187112-17-0, CHF 1909 **187112-22-7**, EF 40
187112-23-8, EN 105 **187112-26-1**, FPL 64170
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HX 0386 **187112-32-9**, L 691816 **187112-33-0**, Linazolast
187112-35-2, LY 280810 **187112-36-3**, MM 7002
187112-41-0, P 8892 **187112-42-1**, p 8977
187112-43-2, PD 136005 **187112-44-3**, PD 145246
187112-47-6, R 840 **187112-50-1**, RU 46057 187112-51-2,
RU 54808 **187112-52-3**, SL 81-0433 **187112-54-5**, SS 81OH
187112-56-7, Tanabe 757 187112-57-8, Tanabe 799 **187112-58-9**,
TMK 685 **187112-59-0**, TZI 2721 **187112-62-5**, WAY 125007
187112-64-7, ZD 7717 **187112-65-8**, ZM 216800

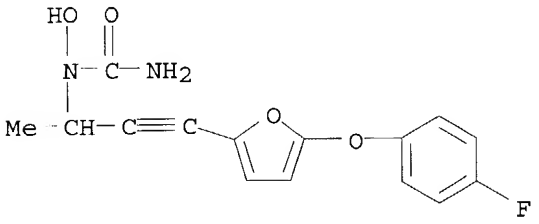
193739-23-0, CMI 392 **195215-27-1**, Carbazoycin c
195215-52-2, RG 5901A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of inflammation and inflammation-related disorders with a combination of a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor)

IT **99-91-2 321-28-8**, 2-Fluoroanisole **383-63-1**, Ethyl trifluoroacetate **454-31-9**, Ethyl difluoroacetate **27918-19-0**, 4-Sulfonamidophenylhydrazine hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(treatment of inflammation and inflammation-related disorders with a combination of a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor)

IT **455-91-4P 18931-60-7P 170570-77-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(treatment of inflammation and inflammation-related disorders with a combination of a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor)

IT **141579-67-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(treatment of inflammation and inflammation-related disorders with a combination of a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor)

RN 141579-67-1 HCAPLUS
CN Urea, N-[3-[5-(4-fluorophenoxy)-2-furanyl]-1-methyl-2-propynyl]-N-hydroxy- (9CI) (CA INDEX NAME)



IT **141579-67-1P 169590-41-4P 170569-86-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(treatment of inflammation and inflammation-related disorders with a combination of a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor)

IT **341-88-8**, KF 8940 **4737-26-2**, Isoflavan **27686-84-6**, Masoprocol **34334-69-5**, Cirsiliol **36441-32-4**, DuP 654 **46721-85-1**, CBS 1114 **60284-71-1**, AHR 5333 **75139-38-7**, Carbazomycin B **79916-77-1**, Forsythiaside **80809-81-0**, Docebenone **87660-25-1**, ONO 5349 **91431-42-4**, Lonapalene **92532-05-3**, Rev 5367 **93211-49-5**, L 651392 **96314-49-7**, TEI 8005 **96920-48-8**, TMK 992 **96928-53-9**, TMK 919 **99107-52-5**, Bunaprolast **99134-29-9**, L 651896 **99318-09-9**, QA 208-199

100035-75-4, Evandamine **101335-99-3**, Eprovafen
101618-31-9, TMK 789 **101619-08-3**, TMK 781
101619-11-8, TMK 777 **101910-24-1**, PF 5901
102612-16-8, L 656224 **103141-09-9**, FPL 62064
103475-41-8, Tepoxalin **104007-80-9**, TZI 41127
104153-37-9, Rilopirox **105357-17-3**, SC 41661A
107008-29-7, L 652343 **107746-52-1**, E 5110
107889-32-7, LY 178002 **110033-17-5**, WY 47288
110406-33-2 **110545-79-4**, SCH 40120 **111406-87-2**
, Zileuton **111525-11-2**, A 63162 **111908-94-2**, SK&F
104351 **111908-95-3**, SK&F 104493 **111974-60-8**, WY 48252
112344-52-2, Flobufen **114832-13-2**, CGS 8515
114917-95-2, BMY 30094 **115255-10-2**, ONO-LP 219
115255-23-7, ONO-LP 269 **115816-05-2**, BI-L 93BS
117574-40-0, CV 6504 **118414-82-7**, L 663536
118420-47-6, AL 3264 **119256-94-9**, FR 110302
120164-49-0, E 6080 **120210-48-2**, Tenidap
120602-97-3, RG 6866 **121135-51-1** **121412-39-3**,
CGS 21595 **121502-05-4**, PD 127443 **122454-69-7**, SK&F
105809 **122610-85-9**, A 65260 **123016-21-7**, WY 50295
123606-23-5, A 69412 **125721-82-6**, BIL 226XX
125722-16-9, Enofelast **127245-22-1**, BF 389
127378-46-5, CI 987 **127481-38-3**, L 674636
128253-31-6, Bay-x-1005 **129424-08-4**, ICI 211965
130116-16-4, CI 986 **130838-15-2**, Y 19432
131817-86-2, CGS 22745 **132392-65-5**, LY 269415
132734-43-1, LY 233569 **132956-22-0**, Enazadrem phosphate
133174-26-2, L 670630 **133430-69-0**, ETH 615
134470-36-3, BW-B 218C **134470-38-5**, BW-B 70C
134822-78-9, CGS 23885 **134823-10-2**, CGS 24891
135133-84-5, SC 45662 **135872-69-4**, WAY 120739
135872-94-5, WAY 121520 **138331-04-1**, R 68151
139149-55-6, SB 202235 **139340-56-0**, CI 1004
140841-32-3 **141579-54-6**, A 76745 **141579-87-5**,
A 79175 **143964-80-1**, F 1322 **145096-30-6**, E 3040
146935-39-9, Epocarbazolin a **147030-01-1**, MK 591
147317-96-2, Nitrosoxacin A **147497-10-7**, CGS 26529
147936-06-9, L 699333 **148915-76-8**, BU 4601A
149539-02-6, BI-L 357 **150693-65-5**, Lagunamycin
153950-29-9, A 121798 **154214-70-7**, R 85355
154355-76-7, ABT 761 **155944-23-3**, ZM 230487
156897-06-2, ML 3000 **158930-07-5**, L 739010
187112-03-4, A 72694 **187112-04-5**, a 80263
187112-09-0, Bay-q-1531 **187112-10-3**, BF 397
187112-11-4, BW 4C **187112-12-5**, BW 70C
187112-17-0, CHF 1909 **187112-22-7**, EF 40
187112-23-8, EN 105 **187112-26-1**, FPL 64170
187112-28-3, GR 80907 **187112-30-7**, HX 0386
187112-32-9, L 691816 **187112-33-0**, Linazolast
187112-35-2, LY 280810 **187112-36-3**, MM 7002
187112-41-0, P 8892 **187112-42-1**, p 8977
187112-43-2, PD 136005 **187112-44-3**, PD 145246
187112-47-6, R 840 **187112-50-1**, RU 46057
187112-52-3, SL 81-0433 **187112-54-5**, SS 81OH
187112-58-9, TMK 685 **187112-59-0**, TZI 2721
187112-62-5, WAY 125007 **187112-64-7**, ZD 7717
187112-65-8, ZM 216800 **193739-23-0**, CMI 392
195215-27-1, Carbazoycin c **195215-52-2**, RG 5901A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

(Uses)
(treatment of inflammation and inflammation-related disorders with a combination of a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor)

IT **99-91-2 321-28-8**, 2-Fluoroanisole **383-63-1**, Ethyl trifluoroacetate **454-31-9**, Ethyl difluoroacetate **27918-19-0**, 4-Sulfonamidophenylhydrazine hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(treatment of inflammation and inflammation-related disorders with a combination of a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor)

IT **455-91-4P 18931-60-7P 170570-77-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(treatment of inflammation and inflammation-related disorders with a combination of a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor)

REFERENCE COUNT: 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L199 ANSWER 19 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:608551 HCAPLUS
DOCUMENT NUMBER: 133:213151
TITLE: Pharmaceutical compositions and methods for improved delivery of hydrophobic therapeutic agents
INVENTOR(S): Patel, Manesh V.; Chen, Feng-Jing
PATENT ASSIGNEE(S): Lipocine, Inc., USA
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050007	A1	20000831	WO 2000-US165	20000105
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6294192	B1	20010925	US 1999-258654	19990226
AU 2000022242	A5	20000914	AU 2000-22242	20000105
AU 771659	B2	20040401		
NZ 513810	A	20010928	NZ 2000-513810	20000105
EP 1158959	A1	20011205	EP 2000-901394	20000105
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537317	T2	20021105	JP 2000-600619	20000105

PRIORITY APPLN. INFO.: US 1999-258654 A 19990226
WO 2000-US165 W 20000105

AB The present invention relates to triglyceride-free pharmaceutical compns. for delivery of hydrophobic therapeutic agents. Compns. of the present invention include a hydrophobic therapeutic agent and a carrier, where the carrier is formed from a combination of a hydrophilic surfactant and a

hydrophobic surfactant. Upon dilution with an aqueous solvent, the composition forms
a clear, aqueous dispersion of the surfactants containing the therapeutic agent.
The invention also provides methods of treatment with hydrophobic therapeutic agents using these compns. A pharmaceutical composition contained cyclosporin 0.14, Cremophor RH-40 0.41, Arlacel186 0.29, sodium taurocholate 0.26, and propylene glycol 0.46 mg.

IC ICM A61K009-127
ICS A61K009-107; A61K038-13

CC 63-6 (Pharmaceuticals)

IT 50-14-6, Ergocalciferol 50-21-5D, Lactic acid, glycerides 50-24-8, Prednisolone 50-28-2, EStradiol, biological studies 50-70-4, Sorbitol, biological studies 51-48-9, L-Thyroxine, biological studies 52-01-7, Spironolactone 55-98-1, Busulphan 56-81-5, 1,2,3-Propanetriol, biological studies 56-81-5D, Glycerol, polyethylene fatty acid esters 57-10-3, Hexadecanoic acid, biological studies 57-11-4, Octadecanoic acid, biological studies 57-55-6, 1,2-Propanediol, biological studies 57-55-6D, Propylene glycol, ethers 57-83-0, Progesterone, biological studies 57-88-5, Cholesterol, biological studies 57-88-5D, Cholesterol, polyoxyethylene derivs. 60-33-3, 9,12-Octadecadienoic acid (9Z,12Z)-, biological studies 64-17-5, Ethanol, biological studies 66-76-2, Dicoumarol 67-20-9, Nitrofurantoin 67-45-8, Furazolidone 67-63-0, Isopropanol, biological studies 67-96-9, Dihydrotachysterol 67-97-0, Cholecalciferol 69-65-8, Mannitol 71-36-3, Butanol, biological studies 76-57-3, Codeine 76-99-3, Methadone 77-89-4, Acetyl triethylcitrate 77-90-7, Acetyl tributyl citrate 77-92-9D, Citric acid, diglycerides 77-93-0, Triethylcitrate 77-94-1, Tributylcitrate 81-24-3 81-25-4 83-44-3 87-33-2, Isosorbide dinitrate 87-69-4D, Tartaric acid, glycerides, biological studies 90-82-4, Pseudoephedrine 100-51-6, Benzenemethanol, biological studies 102-76-1, Triacetin 104-31-4, Benzonatate 105-37-3, EThyl propionate 105-54-4, Ethyl butyrate 105-60-2, biological studies 105-60-2D, Caprolactam, N-Alkyl derivs. 106-32-1, Ethyl caprylate 107-21-1, 1,2-Ethanediol, biological studies 110-27-0, Isopropyl myristate 111-03-5, Glyceryl monooleate 111-62-6, Crodamol EO 111-90-0, Transcutol 112-80-1, 9-Octadecenoic acid (9Z)-, biological studies 113-15-5, Ergotamine 113-92-8, Chlorpheniramine 115-77-5, biological studies 115-83-3, Pentaerythrityl Tetra stearate 124-07-2, Octanoic acid, biological studies 125-84-8, Aminoglutethimide 126-07-8, Griseofulvin 127-19-5, Dimethylacetamide 128-13-2 141-22-0 142-18-7, Glyceryl monolaurate 142-62-1, Hexanoic acid, biological studies 142-91-6, Isopropyl palmitate 143-07-7, Dodecanoic acid, biological studies 151-41-7, Lauryl sulfate 155-97-5, Pyridostigmine 298-46-4, 5H-Dibenz[b,f]azepine-5-carboxamide 298-57-7, Cinnarizine 298-81-7, Methoxsalen 300-62-9, Amphetamine 302-79-4, Tretinoin 303-49-1, Clomipramine 321-64-2, Tacrine 334-48-5, Decanoic acid 359-83-1, Pentazocine 360-65-6 378-44-9, Betamethasone 404-86-4, Capsaicin 437-38-7, Fentanyl 443-48-1, Metronidazole 463-40-1 474-25-9 475-31-0 511-12-6, Dihydroergotamine 516-35-8 516-50-7 520-85-4, Medroxyprogesterone 542-28-9, δ-Valerolactone 544-35-4, Ethyl linoleate 544-63-8, Tetradecanoic acid, biological studies 577-11-7, Sodium docusate 595-33-5 616-45-5, Pyrrolidone 616-45-5D, Pyrrolidone, N-Alkyl derivs. 623-84-7, Propylene glycol diacetate 640-79-9 675-20-7, 2-Piperidone 872-50-4, N-Methylpyrrolidone, biological studies 1134-47-0, Baclofen 1331-12-0, Propylene glycol monoacetate 1335-71-3, Propylene glycol oleate 1338-39-2, Arlacel 20 1338-43-8, Span 80 1397-89-3, Amphotericin B 1406-16-2, Vitamin D 1406-18-4, Vitamin E 1951-25-3, Amiodarone 1972-08-3, Tetrahydrocannabinol 2687-91-4, N-Ethylpyrrolidone

2687-94-7 2687-96-9 3068-88-0, β-Butyrolactone 3445-11-2
4419-39-0, BeclomethAsone 4759-48-2, Isotretinoin 5104-49-4,
Flurbiprofen 5306-85-4, Dimethyl isosorbide 7261-97-4, Dantrolene
7488-99-5, α Carotene 7664-93-9D, Sulfuric acid, salts alkyl
derivs., biological studies 7689-03-4, Camptothecin 8007-43-0,
Sorbitan sesquioleate 9002-89-5, Polyvinylalcohol 9002-92-0, Brij 30
9002-96-4 9003-39-8, Polyvinylpyrrolidone 9004-65-3, Hydroxypropyl
methylcellulose 9004-74-4, Methoxy polyethylene glycol 9004-81-3,
Polyoxyethylene laurate 9004-95-9, Polyoxyethylene cetyl ether
9004-96-0, PEG-32 oleate 9004-98-2, Polyoxyethylene oleyl ether
9004-99-3, Polyoxyethylene stearate 9005-00-9, Polyoxyethylene stearyl
ether 9005-02-1, Polyoxyethylene dilaurate 9005-07-6, Polyoxyethylene
dioleate 9005-08-7, Polyoxyethylene distearate 9005-32-7D, Alginic
acid, salts 9005-37-2, Propylene glycol alginate 9005-63-4D,
Polyoxyethylene sorbitan, derivs. 9005-63-4D, Polyoxyethylene sorbitan,
fatty acid esters 9005-64-5, Tween 20 9005-65-6, Polysorbate 80
9005-66-7, Tween 40 9005-67-8, Tween 60 9007-48-1, PLUROLOLEIQUECC497
9011-21-6, Polyoxyethylene glyceryl stearate 9016-45-9 9036-19-5
10238-21-8, Glyburide 10540-29-1, Tamoxifen 11103-57-4, Vitamin A
11140-04-8, Imwitor 988 12001-79-5, Vitamin K 12619-70-4, Cyclodextrin
12619-70-4D, Cyclodextrin, derivs. 12619-70-4D, Cyclodextrin,
hydroxypropyl ethers 13081-97-5, Pentaerythrityl di stearate
14440-80-3, Stearoyl-2-lactylate 14605-22-2 15307-86-5, Diclofenac
15574-96-6, Pizotifen 15686-51-8, Clemastine 15687-27-1, Ibuprofen
18559-94-9, Albuterol 19356-17-3, Calcifediol 20594-83-6, Nalbuphine
20830-75-5, Digoxin 21256-18-8, Oxaprozin 21829-25-4, Nifedipine
22882-95-7, Isopropyl linoleate 22916-47-8, Miconazole 23288-49-5,
Probucol 25168-73-4, Sucrose monostearate 25265-75-2, Butanediol
25322-68-3 25322-69-4, Polypropylene glycol 25339-99-5, Sucrose
monolaurate 25523-97-1, Dexchlorpheniramine 25618-55-7D, Polyglycerol,
fatty acid esters 25637-84-7, Glyceryl dioleate 25637-97-2, Sucrose
dipalmitate 25812-30-0, Gemfibrozil 26266-57-9, Sorbitan monopalmitate
26266-58-0, Sorbitan Trioleate 26402-22-2, Glyceryl monocaprate
26402-26-6, Glyceryl monocaprylate 26446-38-8, Sucrose monopalmitate
27154-43-4D, Piperidone, N-Alkyl derivs. 27195-16-0, Sucrose distearate
27203-92-5, TRamadol 27638-00-2, Glyceryl dilaurate 29094-61-9,
Glipizide 29767-20-2, Teniposide 31692-85-0, Glycofurol 32222-06-3,
Calcitriol 33069-62-4, Paclitaxel 33419-42-0, Etoposide 34911-55-2,
Bupropion 36354-80-0, Glyceryl dicaprylate 37321-62-3, Lauroglycol
38304-91-5, Minoxidil 41340-25-4, Etodolac 42924-53-8, Nabumetone
43200-80-2, Zopiclone 49562-28-9, Fenofibrate 49697-38-3, Rimexolone
51333-22-3, Budesonide 51481-61-9, Cimetidine 51938-44-4, Sorbitan
sesquistearate 52581-71-2, Volpo 3 53123-88-9, Sirolimus 53168-42-6,
Myvacet 9-45 53179-11-6, Loperamide 53230-10-7, Mefloquine
53988-07-1, Glyceryl dicaprate 54392-26-6, Sorbitan monoisostearate
54965-21-8, Albendazole 55079-83-9, Acitretin 55142-85-3, Ticlopidine
57107-97-8, Polyoxyethylene glyceryl oleate 59467-70-8, Midazolam
59865-13-3, Cyclosporine 60142-96-3, Gabapentin 61379-65-5,
Rifapentine 61869-08-7 62013-04-1, Dirithromycin 62356-64-3
63590-64-7, Terazosin 63612-50-0, Nilutamide 63675-72-9, Nisoldipine
65271-80-9, Mitoxantrone 65277-42-1, Ketoconazole 68506-86-5,
Vigabatrin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. and methods for improved delivery of
hydrophobic therapeutic agents)

IT 68958-64-5, Polyoxyethylene glyceryl trioleate 69756-53-2, Halofantrine
70288-86-7, Ivermectin 72432-03-2, Miglitol 72559-06-9, Rifabutine
73590-58-6, Omeprazole 73963-72-1, Cilostazol 74103-06-3, Ketorolac
74504-64-6, Polyglyceryl laurate 75706-12-6, Leflunomide 76547-98-3,
Lisinopril 76824-35-6, Famotidine 76963-41-2, Nizatidine

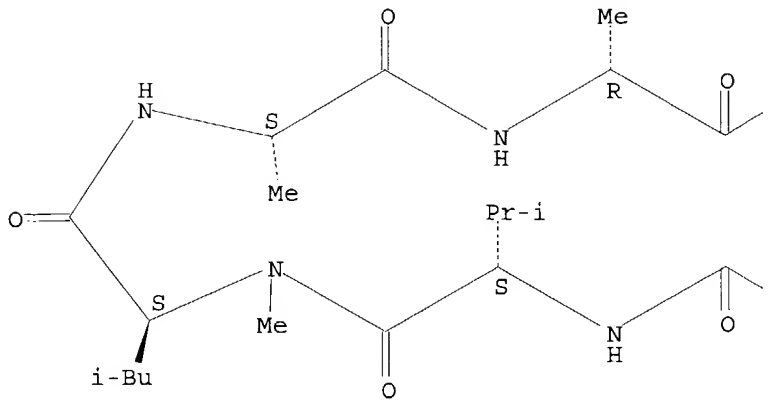
79217-60-0, Cyclosporin 79617-96-2, Sertraline 79794-75-5, Loratadine 79902-63-9, Simvastatin 81093-37-0, Pravastatin 81098-60-4, Cisapride 81103-11-9, Clarithromycin 82626-48-0, Zolpidem 83799-24-0, Fexofenadine 83881-51-0, Cetirizine 83905-01-5, Azithromycin 84057-84-1, Lamotrigine 84371-65-3, Mifepristone 84449-90-1, Raloxifene 84625-61-6, Itraconazole 85721-33-1, Ciprofloxacin 86386-73-4, Fluconazole 86541-75-5, Benazepril 86637-84-5 88150-42-9, Amlodipine 89778-26-7, Toremifene 90357-06-5, Bicalutamide 91161-71-6, Terbinafine 93390-81-9, Fosphenytoin 93413-69-5, Venlafaxine 93479-97-1, Glimepiride 93790-70-6, Cholylsarcosine 93790-72-8 93957-54-1, Fluvastatin 95233-18-4, Atovaquone 97240-79-4, Topiramate 97322-87-7, Troglitazone 97682-44-5, Irinotecan 98319-26-7, Finasteride 101828-21-1, Butenafine 103577-45-3, Lansoprazole 103628-46-2, Sumatriptan 104987-11-3, Tacrolimus 106133-20-4, Tamsulosin 106392-12-5, Ethylene oxide propylene oxide block copolymer 106650-56-0, Sibutramine 107753-78-6, Zafirlukast 111025-46-8, Pioglitazone **111406-87-2**, Zileuton 112965-21-6, Calcipotriene 113665-84-2, Clopidogrel 115103-54-3, Tiagabine 117976-89-3, Rabeprazole 118292-40-3, Tazarotene 120014-06-4, Donepezil 121679-13-8, Naratriptan 122320-73-4, Rosiglitazone 123948-87-8, Topotecan 127779-20-8, Saquinavir 129497-78-5, Verteporfin 131918-61-1, Paricalcitol 133040-01-4, Eprosartan 134523-00-5, Atorvastatin 135062-02-1, Repaglinide 137862-53-4, Valsartan 138402-11-6 139264-17-8, Zolmitriptan 139481-59-7, Candesartan 144034-80-0, Rizatriptan 144494-65-5, Tirofiban 144701-48-4, Telmisartan 145599-86-6, Cerivastatin 145941-26-0, Oprelvekin 147059-72-1, Trovafloxacin 150372-93-3, Polyoxyethylene glyceryl laurate 153559-49-0, Targretin 154598-52-4, Efavirenz 155213-67-5, Ritonavir 156259-68-6, Capmul mcm 158747-02-5, Frovatriptan 158966-92-8, Montelukast 159989-64-7, Nelfinavir **162011-90-7**, Rofecoxib 169590-42-5, Celecoxib 171599-83-0, Sildenafil citrate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. and methods for improved delivery of hydrophobic therapeutic agents)

IT **59865-13-3**, Cyclosporine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. and methods for improved delivery of hydrophobic therapeutic agents)

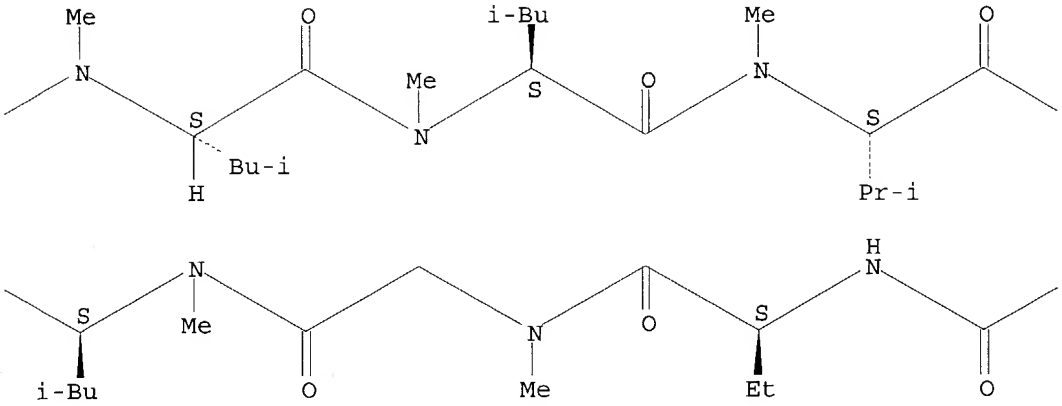
RN 59865-13-3 HCAPLUS
CN Cyclosporin A (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

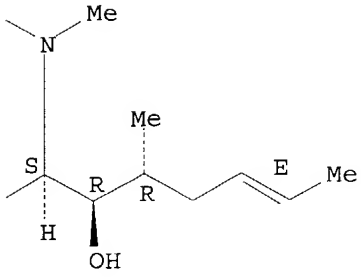
PAGE 1-A



PAGE 1-B



PAGE 1-C



IT **59865-13-3**, Cyclosporine **79217-60-0**, Cyclosporin

111406-87-2, Zileuton **162011-90-7**, Rofecoxib
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. and methods for improved delivery of hydrophobic therapeutic agents)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L199 ANSWER 20 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:744944 HCAPLUS
DOCUMENT NUMBER: 130:10625
TITLE: COX-2-selective carprofen and related compounds for treating pain and inflammation in dogs
INVENTOR(S): Lundy, Kristin Marie; Ricketts, Anthony Paul
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9850033	A1	19981112	WO 1998-IB662	19980501
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9869321	A1	19981127	AU 1998-69321	19980501
EP 988034	A1	20000329	EP 1998-915041	19980501
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
BR 9808720	A	20000711	BR 1998-8720	19980501
JP 2000513020	T2	20001003	JP 1998-547869	19980501
NZ 500183	A	20020426	NZ 1998-500183	19980501
NZ 516914	A	20030829	NZ 1998-516914	19980501
ZA 9803722	A	19991104	ZA 1998-3722	19980504
MX 9910148	A	20000228	MX 1999-10148	19991104
US 2003212123	A1	20031113	US 2003-422220	20030424

PRIORITY APPLN. INFO.:
US 1997-45635P P 19970505
NZ 1998-500183 A1 19980501
WO 1998-IB662 W 19980501
US 1999-308955 A3 19990527

OTHER SOURCE(S): MARPAT 130:10625

AB The invention relates to treating or preventing inflammatory processes and diseases in dogs associated with the activity of inducible cyclooxygenase-2 (COX-2), while at the same time reducing or eliminating undesirable side effects associated with simultaneous inhibition of the activity of constitutive cyclooxygenase-1 (COX-1) by selectively inhibiting COX-2 activity with reference to COX-1 activity, wherein the selectivity ratio or COX-2:COX-1 activity inhibition is at least 3:1 based on ex vivo inhibition levels measured in whole blood. The inhibitor is a member selected from the group of antiinflammatory compds. consisting essentially of salicylic acid derivs., p-aminophenol derivs., indole and indene acetic acids, heteroaryl acetic acids, arylpropionic acids, anthranilic acids, enolic acids, and alkanones; the inhibitor in particular is comprised of

the (+)(S)-enantiomer of 6-chloro-α-methyl-9H-carbazole-2-acetic acid.

IC ICM A61K031-40

CC 1-7 (Pharmacology)

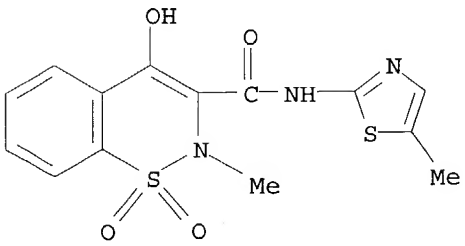
IT 50-33-9, Phenylbutazone, biological studies 50-78-2, Aspirin 53-86-1, Indomethacin 61-68-7, Mefenamic acid 530-78-9, Flufenamic acid 644-62-2, Meclofenamic acid 4394-00-7, Niflumic acid 5104-49-4, Flurbiprofen 5728-52-9, Felbinac 13710-19-5, Tolfenamic acid 15307-86-5, Diclofenac 15687-27-1, Ibuprofen 22071-15-4, Ketoprofen 22131-79-9, Alclofenac 22204-53-1, Naproxen 23981-47-7, 6-Methoxy-2-naphthylacetic acid 36322-90-4, Piroxicam 38677-85-9, Flunixin 41340-25-4, Etodolac 51803-78-2, Nimesulide 52263-83-9, (R)-Carprofen 71109-09-6, Vedaprofen **71125-38-7**, Meloxicam **120210-48-2**, Tenidap **123653-11-2**, NS-398 135202-79-8, Ilonidap
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(COX-2-selective carprofen and related compds. for treating pain and inflammation in dogs, and comparative inhibition of COX-1 and -2 by carprofen and other NSAIDs)

IT 52-67-5, Penicillamine 57-22-7, Vincristine 57-66-9, Probenecid 57-96-5, Sulfinpyrazone 59-05-2, Methotrexate 64-86-8, Colchicine 118-42-3, Hydroxychloroquine 315-30-0, Allopurinol 446-86-6, Azathioprine 865-21-4, Vinblastine 3562-84-3, Benzbromarone 7440-57-5D, Gold, aurothio derivs., biological studies **59865-13-3**, Cyclosporine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(COX-2-selective carprofen and related compds. for treating pain and inflammation in dogs, and use with other agents)

IT **71125-38-7**, Meloxicam
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(COX-2-selective carprofen and related compds. for treating pain and inflammation in dogs, and comparative inhibition of COX-1 and -2 by carprofen and other NSAIDs)

RN 71125-38-7 HCAPLUS

CN 2H-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-, 1,1-dioxide (9CI) (CA INDEX NAME)



IT **71125-38-7**, Meloxicam **120210-48-2**, Tenidap **123653-11-2**, NS-398
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(COX-2-selective carprofen and related compds. for treating pain and inflammation in dogs, and comparative inhibition of COX-1 and -2 by carprofen and other NSAIDs)

IT **59865-13-3**, Cyclosporine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(COX-2-selective carprofen and related compds. for treating pain and inflammation in dogs, and use with other agents)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L199 ANSWER 21 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:562996 HCAPLUS
DOCUMENT NUMBER: 127:239123
TITLE: Combinations having immunosuppressive effects, containing cyclooxygenase-2-inhibitors and 5-lipoxygenase inhibitors
INVENTOR(S): Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
PATENT ASSIGNEE(S): G.D. Searle and Co., USA; Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9729776	A1	19970821	WO 1997-US1558	19970212
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2246265	AA	19970821	CA 1997-2246265	19970212
AU 9718505	A1	19970902	AU 1997-18505	19970212
EP 888127	A1	19990107	EP 1997-904133	19970212
EP 888127	B1	20011212		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2000504723	T2	20000418	JP 1997-529363	19970212
AT 210461	E	20011215	AT 1997-904133	19970212
PT 888127	T	20020531	PT 1997-904133	19970212
ES 2169351	T3	20020701	ES 1997-904133	19970212
US 6376528	B1	20020423	US 1999-430072	19991018
US 2002143033	A1	20021003	US 2002-98644	20020315

PRIORITY APPLN. INFO.:
US 1996-600622 A1 19960213
WO 1997-US1558 W 19970212
US 1998-189463 B1 19981110
US 1999-430072 A3 19991018

OTH RPAT 127:239123

AB Applicants oxygenase-2 inhibitor and a 5-lipoxygenase inhibitor useful in reducing recipient rejection of d for treatment of autoimmune diseases. xyphenyl)-3-(difluoromethyl)-1H-pyrazol-1- and N'-[3-[5-(4-fluorophenoxy)-2-furyl]-1-methyl-2-

propynyl]-N'-hydroxyurea were prepared and a combination of these 2 compds. showed a delay in rejection time of skin grafts while treatment alone of each of these compds. resulted in no prolongation of graft survival.

IC ICM A61K045-06

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 15

IT **134470-38-5**, BW-B 70C
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BW-B 70C; cyclooxygenase-2 and 5-lipoxygenase inhibitor combinations with immunosuppressive effects)

IT **187112-47-6**, R 840
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(R 840; cyclooxygenase-2 and 5-lipoxygenase inhibitor combinations with immunosuppressive effects)

IT **141579-67-1P**, A-78773 **169590-41-4P 170569-86-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclooxygenase-2 and 5-lipoxygenase inhibitor combinations with immunosuppressive effects)

IT **99-91-2**, 4'-Chloroacetophenone **321-28-8**, 2-Fluoroanisole **383-63-1**, Ethyl trifluoroacetate **454-31-9**, Ethyl difluoroacetate **27918-19-0**, 4-Sulfonamidophenylhydrazine hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(cyclooxygenase-2 and 5-lipoxygenase inhibitor combinations with immunosuppressive effects)

IT **455-91-4P**, 3'-Fluoro-4'-methoxyacetophenone **18931-60-7P 170570-77-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(cyclooxygenase-2 and 5-lipoxygenase inhibitor combinations with immunosuppressive effects)

IT **341-88-8**, KF-8940 **4737-26-2**, Isoflavan
27686-84-6, Masoprocol **34334-69-5**, Cirsiliol
36441-32-4, DuP-654 **46721-85-1**, CBS-1114
60284-71-1, AHR-5333 **71125-38-7**, Meloxicam
75139-38-7, Carbazomycin B **79916-77-1**, Forsythiaside
80809-81-0, Docebenone **80937-31-1**, Flosulide
87660-25-1, ONO 5349 **88149-94-4**, Dup 697
91431-42-4, Lonapalene **92532-05-3**, Rev 5367
93014-16-5 93211-49-5, L-651392 **96314-49-7**,
TEI-8005 **96920-48-8**, TMK 992 **96928-53-9**, TMK-919
99107-52-5, Bunaprolast **99134-29-9**, L-651896
99318-09-9, QA-208-199 **100035-75-4**, Evandamine
101335-99-3, Eprovafen **101618-31-9**, TMK 789
101619-08-3, TMK 781 **101619-11-8**, TMK-777
101910-24-1, PF-5901 **102612-16-8**, L-656224
103141-09-9, FPL 62064 **103475-41-8**, Tepoxalin
104007-80-9, TZI-41127 **104153-37-9**, Rilopirox
105357-17-3, SC-41661A **107008-29-7**, L-652343
107746-52-1, E 5110 **107889-32-7**, LY-178002
110033-17-5, WY 47288 **110406-33-2 110545-79-4**,
SCH 40120 **111406-87-2**, Zileuton **111525-11-2**, A-63162
111908-94-2, SK&F-104351 **111908-95-3**, SK&F-104493
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114832-13-2, CGS 8515 **114917-95-2**, BMY-30094
115255-10-2, ONO-LP 219 **115255-23-7**, ONO-LP 269
115816-05-2, BI-L-93BS **117574-40-0**, CV-6504
118414-82-7, MK-886 **118420-47-6**, Tagorizine

119256-94-9, FR 110302 **120164-49-0**, E-6080
120210-48-2, Tenidap **120602-97-3**, RG-6866
121135-51-1 121412-39-3, CGS-21595 **121502-05-4**
, PD-127443 **122454-69-7**, SK&F-105809 **122610-85-9**,
A-65260 **123016-21-7**, WY-50295 **123606-23-5**, A-69412
123653-11-2, NS-398 **125721-82-6**, BIL 226XX
125722-16-9, Enofelast **127245-22-1**, BF-389
127378-46-5, CI 987 **127481-38-3**, L-674636
128253-31-6, BAY-X-1005 **129424-08-4**, ICI-211965
130116-16-4, CI-986 **130211-54-0**, T-799
130211-75-5, T-757 **130838-15-2**, Y-19432
131817-86-2, CGS 22745 **132392-65-5**, LY-269415
132734-43-1, LY-233569 **132956-22-0**, Enazadrem phosphate
133174-26-2, L-670630 **133430-69-0**, ETH-615
134470-36-3, BW-B 218C **134822-78-9**, CGS-23885
134823-10-2, CGS 24891 **135133-84-5**, SC-45662
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141579-54-6, A 76745 **141579-87-5**, A-79175
143964-80-1, F-1322 **145096-30-6**, E 3040
146935-39-9, Epocarbazolin A **147030-01-1**, MK-591
147317-96-2, Nitrosoxacin A **147497-10-7**, CGS 26529
147936-06-9, L 699333 **148915-76-8**, BU 4601A
149539-02-6, BI-L-357 **150693-65-5**, Lagunamycin
153950-29-9, A 121798 **154214-70-7**, R-85355
154355-76-7, ABT 761 **155944-23-3**, ZM-230487
156897-06-2, ML-3000 **158930-07-5**, L 739010
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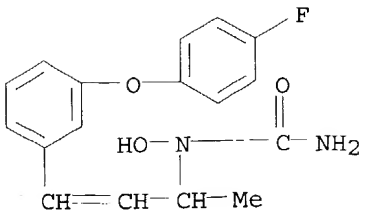
177660-92-3 181695-72-7 185344-51-8
185344-55-2 187112-03-4, A 72694 **187112-04-5**,
A-80263 **187112-09-0**, Bay-q-1531 **187112-10-3**, BF-397
187112-11-4, BW 4C **187112-12-5**, BW-70C
187112-17-0, CHF-1909 **187112-22-7**, EF-40
187112-23-8, EN-105 **187112-26-1**, FPL-64170
187112-28-3, GR-80907 **187112-30-7**, HX 0386
187112-32-9, L-691816 **187112-33-0**, Linazolast
187112-35-2, LY-280810 **187112-36-3**, MM-7002
187112-41-0, P 8892 **187112-42-1**, P 8977
187112-43-2, PD-136005 **187112-44-3**, PD-145246
187112-50-1, RU-46057 **187112-52-3**, SL-81-0433
187112-54-5, SS 81OH **187112-58-9**, TMK 685
187112-59-0, TZI-2721 **187112-62-5**, WAY-125007
187112-64-7, ZD 7717 **187112-65-8**, ZM-216800
193739-23-0, CMI-392 **195061-34-8 195065-56-6**
195065-57-7 195215-27-1, Carbazoycin C
195215-52-2, RG 5901A
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase-2 and 5-lipoxygenase inhibitor combinations with immunosuppressive effects)

IT **134470-38-5**, BW-B 70C
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BW-B 70C; cyclooxygenase-2 and 5-lipoxygenase inhibitor combinations with immunosuppressive effects)

RN 134470-38-5 HCAPLUS

CN Urea, N-[3-[3-(4-fluorophenoxy)phenyl]-1-methyl-2-propenyl]-N-hydroxy-(9CI) (CA INDEX NAME)



IT **134470-38-5**, BW-B 70C
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BW-B 70C; cyclooxygenase-2 and 5-lipoxygenase inhibitor combinations with immunosuppressive effects)

IT **187112-47-6**, R 840
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(R 840; cyclooxygenase-2 and 5-lipoxygenase inhibitor combinations with immunosuppressive effects)

IT **141579-67-1P**, A-78773 **169590-41-4P 170569-86-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclooxygenase-2 and 5-lipoxygenase inhibitor combinations with immunosuppressive effects)

IT **99-91-2**, 4'-Chloroacetophenone **321-28-8**, 2-Fluoroanisole **383-63-1**, Ethyl trifluoroacetate **454-31-9**, Ethyl difluoroacetate **27918-19-0**, 4-Sulfonamidophenylhydrazine hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(cyclooxygenase-2 and 5-lipoxygenase inhibitor combinations with immunosuppressive effects)

IT **455-91-4P**, 3'-Fluoro-4'-methoxyacetophenone **18931-60-7P 170570-77-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(cyclooxygenase-2 and 5-lipoxygenase inhibitor combinations with immunosuppressive effects)

IT **341-88-8**, KF-8940 **4737-26-2**, Isoflavan **27686-84-6**, Masoprocol **34334-69-5**, Cirsiliol **36441-32-4**, DuP-654 **46721-85-1**, CBS-1114 **60284-71-1**, AHR-5333 **71125-38-7**, Meloxicam **75139-38-7**, Carbazomycin B **79916-77-1**, Forsythiaside **80809-81-0**, Docebenone **80937-31-1**, Flosulide **87660-25-1**, ONO 5349 **88149-94-4**, Dup 697 **91431-42-4**, Lonapalene **92532-05-3**, Rev 5367 **93014-16-5 93211-49-5**, L-651392 **96314-49-7**, TEI-8005 **96920-48-8**, TMK 992 **96928-53-9**, TMK-919 **99107-52-5**, Bunaprolast **99134-29-9**, L-651896 **99318-09-9**, QA-208-199 **100035-75-4**, Evandamine **101335-99-3**, Eprovafen **101618-31-9**, TMK 789 **101619-08-3**, TMK 781 **101619-11-8**, TMK-777 **101910-24-1**, PF-5901 **102612-16-8**, L-656224 **103141-09-9**, FPL 62064 **103475-41-8**, Tepoxalin **104007-80-9**, TZI-41127 **104153-37-9**, Rilopirox **105357-17-3**, SC-41661A **107008-29-7**, L-652343 **107746-52-1**, E 5110 **107889-32-7**, LY-178002 **110033-17-5**, WY 47288 **110406-33-2 110545-79-4**, SCH 40120 **111406-87-2**, Zileuton **111525-11-2**, A-63162 **111908-94-2**, SK&F-104351 **111908-95-3**, SK&F-104493

111974-60-8, WY-48252 **112344-52-2**, Flobufen
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115255-10-2, ONO-LP 219 **115255-23-7**, ONO-LP 269
115816-05-2, BI-L-93BS **117574-40-0**, CV-6504
118414-82-7, MK-886 **118420-47-6**, Tagorizine
119256-94-9, FR 110302 **120164-49-0**, E-6080
120210-48-2, Tenidap **120602-97-3**, RG-6866
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127378-46-5, CI 987 **127481-38-3**, L-674636
128253-31-6, BAY-X-1005 **129424-08-4**, ICI-211965
130116-16-4, CI-986 **130211-54-0**, T-799
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131817-86-2, CGS 22745 **132392-65-5**, LY-269415
132734-43-1, LY-233569 **132956-22-0**, Enazadrem phosphate
133174-26-2, L-670630 **133430-69-0**, ETH-615
134470-36-3, BW-B 218C **134822-78-9**, CGS-23885
134823-10-2, CGS 24891 **135133-84-5**, SC-45662
135872-69-4, WAY 120739 **135872-94-5**, WAY 121520
138331-04-1, R-68151 **139149-55-6**, SB-202235
139340-56-0, CI-1004 **140841-32-3**, ZD02138
141579-54-6, A 76745 **141579-87-5**, A-79175
143964-80-1, F-1322 **145096-30-6**, E 3040
146935-39-9, Epocarbazolin A **147030-01-1**, MK-591
147317-96-2, Nitrosoxacin A **147497-10-7**, CGS 26529
147936-06-9, L 699333 **148915-76-8**, BU 4601A
149539-02-6, BI-L-357 **150693-65-5**, Lagunamycin
153950-29-9, A 121798 **154214-70-7**, R-85355
154355-76-7, ABT 761 **155944-23-3**, ZM-230487
156897-06-2, ML-3000 **158930-07-5**, L 739010
162011-90-7 **177660-77-4** **177660-80-9**
177660-92-3 **181695-72-7** **185344-51-8**
185344-55-2 **187112-03-4**, A 72694 **187112-04-5**,
A-80263 **187112-09-0**, Bay-q-1531 **187112-10-3**, BF-397
187112-11-4, BW 4C **187112-12-5**, BW-70C
187112-17-0, CHF-1909 **187112-22-7**, EF-40
187112-23-8, EN-105 **187112-26-1**, FPL-64170
187112-28-3, GR-80907 **187112-30-7**, HX 0386
187112-32-9, L-691816 **187112-33-0**, Linazolast
187112-35-2, LY-280810 **187112-36-3**, MM-7002
187112-41-0, P 8892 **187112-42-1**, P 8977
187112-43-2, PD-136005 **187112-44-3**, PD-145246
187112-50-1, RU-46057 **187112-52-3**, SL-81-0433
187112-54-5, SS 81OH **187112-58-9**, TMK 685
187112-59-0, TZI-2721 **187112-62-5**, WAY-125007
187112-64-7, ZD 7717 **187112-65-8**, ZM-216800
193739-23-0, CMI-392 **195061-34-8** **195065-56-6**
195065-57-7 **195215-27-1**, Carbazoycin C
195215-52-2, RG 5901A
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase-2 and 5-lipoxygenase inhibitor combinations with immunosuppressive effects)

L199 ANSWER 22 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:557660 HCAPLUS
DOCUMENT NUMBER: 127:239120
TITLE: Compositions comprising a cyclooxygenase-2 inhibitor

and a leukotriene B4 receptor antagonist for reducing transplant rejection

INVENTOR(S): Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary

PATENT ASSIGNEE(S): G.D. Searle and Co., USA; Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary

SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9729775	A1	19970821	WO 1997-US1422	19970211
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TR, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ				
RW: KE, LS, MW, SD, SZ, UG, IE, IT, LU, MC, NL, PT, MR, NE, SN, TD, TG				FI, FR, GB, GR, CM, GA, GN, ML,
CA 2246356	AA	19970821		19970211
AU 9722500	A1	19970902		19970211
EP 880362	A1	19981202		19970211
R: AT, BE, CH, DE, DK, ES,				NL, SE, PT, IE, FI
JP 2000505445	T2	20000509		19970211
US 6172096	B1	20010109	US 1998-75633	19980511
US 6617345	B1	20030909	US 2000-659299	20000912
US 2004106668	A1	20040603	US 2003-617222	20030710

Applicants

PRIORITY APPLN. INFO.:

US 1996-600580	A1	19960213
WO 1997-US1422	W	19970211
US 1998-75633	A3	19980511
US 2000-659299	A3	20000912

OTHER SOURCE(S): MARPAT 127:239120

AB Treatment with a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist is described as being useful in reducing recipient rejection of transplanted organs and for treatment of autoimmune diseases.

IC ICM A61K045-06
ICS A61K031-00; A61K031-10; A61K031-18; A61K038-13

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 2

IT **127378-46-5**, CI 987
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CI 987; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT **170569-86-5P** 195061-35-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT 32222-06-3, Calcitriol **59865-13-3**, Cyclosporin a 60940-34-3, Ebselen **71125-38-7**, Meloxicam **79217-60-0**, Cyclosporin **80937-31-1**, Flosulide 85259-71-8, BAY 0-8276 **88149-94-4**, Dup 697 **93014-16-5** **101910-24-1**, PF-5901 110501-66-1, TMK-688 **111908-95-3**, SK&F-104493 117423-74-2, LY

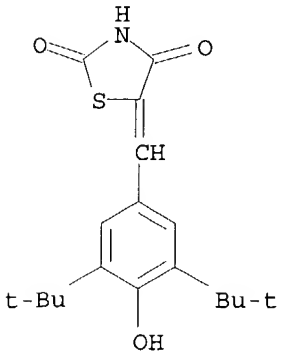
223982 117423-95-7, LY 213024 117690-79-6, LY-255283
118414-82-7, MK-886 119261-58-4, TEI 1338 120072-59-5,
SC-41930 **123653-11-2**, NS-398 **128253-31-6**, Bay-x-1005
130211-75-5, T-757 **132734-43-1**, LY 233569
133430-69-0, ETH-615 134578-96-4, ONO LB457 135199-82-5, LY
264086 135893-33-3, PF 10042 136326-31-3, WAY 121006 141059-52-1,
SC-51146 141748-00-7, RP 69698 141835-49-6, RG 14893 142422-79-5, RP
66153 146461-98-5, SM 15178 **147030-01-1**, MK-591 147398-01-4,
CGS-25019C 147432-77-7, Ontazolast 150399-22-7, SB-201993
153034-77-6, LY 292728 153633-01-3, SC-53228 154413-61-3, SB-209247
158081-99-3, Pfizer 105696 158089-95-3, S 2474 161172-51-6, LY-293111
162011-83-8 **162011-90-7** 162153-46-0, SC 52798
169590-41-4 169590-42-5 **177660-77-4**
177660-80-9 **177660-92-3** 180208-37-1, SB-201146
181695-72-7 **185344-51-8** **185344-55-2**
186912-85-6, ONO-LB-448 186912-92-5, RP 66364 186912-94-7, SC-50505
195061-34-8 195215-25-9, BPC 15 195215-47-5, MNX 160
195215-55-5, SR 2566
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT **99-91-2**, 4'-Chloroacetophenone **383-63-1**, Ethyl trifluoroacetate **454-31-9**, Ethyl difluoroacetate **27918-19-0**, 4-Sulfonamidophenyl hydrazine hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT **455-91-4P**, 3'-Fluoro-4'-methoxyacetophenone **18931-60-7P** **170570-77-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT **127378-46-5**, CI 987
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CI 987; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

RN 127378-46-5 HCAPLUS
CN 2,4-Thiazolidinedione, 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]- (9CI) (CA INDEX NAME)



IT **127378-46-5**, CI 987
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CI 987; compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT **170569-86-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT **59865-13-3**, Cyclosporin a **71125-38-7**, Meloxicam
79217-60-0, Cyclosporin **80937-31-1**, Flosulide
88149-94-4, Dup 697 **93014-16-5 101910-24-1**,
PF-5901 **111908-95-3**, SK&F-104493 **118414-82-7**, MK-886
123653-11-2, NS-398 **128253-31-6**, Bay-x-1005
130211-75-5, T-757 **132734-43-1**, LY 233569
133430-69-0, ETH-615 **147030-01-1**, MK-591
162011-90-7 169590-41-4 177660-77-4
177660-80-9 177660-92-3 181695-72-7
185344-51-8 185344-55-2 195061-34-8
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT **99-91-2**, 4'-Chloroacetophenone **383-63-1**, Ethyl trifluoroacetate **454-31-9**, Ethyl difluoroacetate
27918-19-0, 4-Sulfonamidophenyl hydrazine hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

IT **455-91-4P**, 3'-Fluoro-4'-methoxyacetophenone **18931-60-7P**
170570-77-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(compns. comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection)

L199 ANSWER 23 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:174992 HCAPLUS
DOCUMENT NUMBER: 126:166479
TITLE: Compositions com... e-2 inhibitor and a 5-lipoxy... tment of inflammation an... isorders
INVENTOR(S): Isakson, Peter ... egory, Susan A.
PATENT ASSIGNEE(S): G.D. Searle and
SOURCE: PCT Int. Appl., CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

Applicants

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9641626	A1	19961227	WO 1996-US10106	19960611

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN

CA 2224517	AA	19961227	CA 1996-2224517	19960611	
AU 9661117	A1	19970109	AU 1996-61117	19960611	
EP 833622	A1	19980408	EP 1996-918465	19960611	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI					
JP 11507670	T2	19990706	JP 1997-503273	19960611	

PRIORITY APPLN. INFO.: US 1995-489472 A 19950612
WO 1996-US10106 W 19960611

OTHER SOURCE(S): MARPAT 126:166479

AB Combinations of a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor are described for treatment of inflammation and inflammation-related disorders. Preparation of e.g. 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is described., as are pharmaceutical formulations and activity against collagen-induced arthritis in mice.

IC ICM A61K031-00
ICS A61K031-10; A61K031-18

CC 1-7 (Pharmacology)
Section cross-reference(s): 28, 63

IT **141579-54-6**, A 76745
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(A 76745; cyclooxygenase-2 inhibitor combination with 5-lipoxygenase inhibitor for treatment of inflammation and inflammation-related disorders, compound preparation, antiarthritic activity and pharmaceutical compns.)

IT **187112-47-6**, R 840 (Pharmaceutical)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(R 840; cyclooxygenase-2 inhibitor combination with 5-lipoxygenase inhibitor for treatment of inflammation and inflammation-related disorders, compound preparation, antiarthritic activity and pharmaceutical compns.)

IT **170569-86-5P** 186887-83-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclooxygenase-2 inhibitor combination with 5-lipoxygenase inhibitor for treatment of inflammation and inflammation-related disorders, compound preparation, antiarthritic activity and pharmaceutical compns.)

IT **341-88-8**, KF-8940 **4737-26-2**, Isoflavan
27686-84-6, Masoprocol **34334-69-5**, Cirsiliol
36441-32-4, DuP-654 **46721-85-1**, CBS-1114 50847-11-5,
Ibudilast **60284-71-1**, AHR-5333 **71125-38-7**, Meloxicam
75139-38-7, Carbazomycin B 78794-60-2 **79916-77-1**,
Forsythiaside **80809-81-0**, Docebenone **87660-25-1**, ONO
5349 **91431-42-4**, Lonapalene **92532-05-3**, Rev 5367
93211-49-5, L-651392 **96314-49-7**, TEI-8005
96920-48-8, TMK 992 **96928-53-9**, TMK-919
99107-52-5, Bunaprolast **99134-29-9**, L-651896
99318-09-9, QA-208-199 **100035-75-4**, Evandamine
101335-99-3, Eprovafen **101618-31-9**, TMK 789
101619-08-3, TMK 781 **101619-11-8**, TMK-777
101910-24-1, PF-5901 **102612-16-8**, L-656224
103141-09-9, FPL 62064 **103475-41-8**, Tepoxalin
104007-80-9, TZI-41127 **104153-37-9**, Rilopirox
105357-17-3, SC-41661A **107008-29-7**, L-652343

107746-52-1, E 5110 **107889-32-7**, LY 178002
108073-62-7, Carbazomycin C **110033-17-5**, WY 47288
110406-33-2 110501-66-1, TMK-688 **110545-79-4**, SCH
40120 **111406-87-2**, Zileuton **111525-11-2**, A 63162
111908-94-2, SK&F-104351 **111908-95-3**, SK&F-104493
111974-60-8, Wy-48252 **112344-52-2**, Flobufen
114832-13-2, CGS-8515 **114917-95-2**, BMY-30094
115255-10-2, ONO-LP 219 **115255-23-7**, ONO-LP 269
115816-05-2, BI-L-93BS **117574-40-0**, CV-6504
118414-82-7, L 663536 **118420-47-6**, AL-3264
119256-94-9, FR 110302 **120164-49-0**, E-6080
120210-48-2, Tenidap **120602-97-3**, RG-6866
121135-51-1, 210-610 **121412-39-3**, CGS-21595
121502-05-4, PD-127443 **122454-69-7**, SK&F-105809
122610-85-9, A-65260 **123016-21-7**, Wy-50295
123606-23-5, A-69412 **123653-11-2**, NS-398 125578-25-8
125721-82-6, BIL 226XX **125722-16-9**, Enofelast
127245-22-1, BF-389 **127378-46-5**, CI 987
127481-38-3, L-674636 **128253-31-6**, Bay-x-1005
129424-08-4, ICI-211965 **130116-16-4**, CI-986
130838-15-2, Y-19432 **131817-86-2**, CGS 22745
132392-65-5, LY-269415 **132734-43-1**, LY-233569
132956-22-0, Enazadrem phosphate **133174-26-2**, L-670630
133430-69-0, ETH-615 **134470-36-3**, BW-B 218C
134470-38-5, BW-B 70C **134822-78-9**, CGS-23885
134823-10-2, CGS 24891 **135133-84-5**, SC-45662
135872-69-4, WAY 120739 **135872-94-5**, WAY 121520
138331-04-1, R-68151 **139149-55-6**, SB-202235
139340-56-0, CI 1004 **140841-32-3**, ZD-2138
141579-67-1, A-78773 **141579-87-5**, A-79175 143809-38-5
143809-39-6 **143964-80-1**, F-1322 **145096-30-6**, E 3040
146935-39-9, Epocarbazolin A **147030-01-1**, MK-591
147317-96-2, Nitrosoxacin A 147432-77-7, Ontazolast
147497-10-7, CGS 26529 **147936-06-9**, L-699333
148915-76-8, BU 4601A **149539-02-6**, BI-L-357
150693-65-5, Lagunamycin 152784-11-7, WILD20 **153950-29-9**
, A 121798 **154214-70-7**, R-85355 **154355-76-7**, ABT 761
155944-23-3, ZM 230487 **156897-06-2**, ML-3000
157630-13-2, MER W8020 **158930-07-5**, L 739010 158959-32-1
158959-33-2 158959-34-3 158959-35-4 158959-37-6 158959-42-3
158959-43-4 158959-46-7 158959-47-8 158959-56-9 159429-69-3
159429-70-6 161435-44-5, CGS-25997 **162011-90-7**, MK 966
162054-19-5 162738-34-3 163303-19-3 163303-25-1 163303-29-5
163303-38-6 165251-89-8 165328-42-7 165328-49-4 165328-51-8
165328-52-9 168299-83-0 168299-90-9 168433-84-9 169154-04-5
169154-07-8 169154-19-2 169154-24-9 **169590-41-4**
169590-42-5 169902-71-0 169902-74-3 169902-75-4 169951-23-9
169951-24-0 169951-25-1 169951-27-3 169951-28-4 170569-31-0
170569-42-3 170569-50-3 170569-87-6 170569-88-7 170569-91-2
170570-05-5 170570-25-9 170570-29-3 170570-31-7 170570-32-8
170570-33-9 170571-71-8 171095-65-1, CMI 568 171888-46-3
173776-67-5 174454-52-5 174470-77-0 175676-91-2 175676-92-3
175677-05-1 175677-06-2 175677-07-3 175677-13-1 175677-14-2
175883-05-3 175883-36-0 177560-19-9 177560-23-5 177560-29-1
177560-30-4 177560-34-8 177560-36-0 177560-38-2 177560-61-1
177660-54-7 177660-55-8 177660-56-9 177660-67-2 177660-72-9
177660-73-0 177660-76-3 **177660-77-4** 177660-78-5
177660-81-0 177660-85-4 177660-89-8 **177660-92-3**
177660-94-5 177661-00-6 177661-01-7 177661-02-8 177661-04-0
177661-06-2 177661-15-3 177661-17-5 177661-18-6 177661-19-7

177661-49-3 177662-22-5 177754-42-6 181627-94-1 181627-96-3
181627-98-5 181628-00-2 **181695-72-7** 181695-81-8
181695-85-2 181696-18-4 181696-33-3 181809-58-5 181809-60-9
181809-63-2 **185344-55-2** 186804-93-3 186887-75-2
186912-76-5, L 752860
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase-2 inhibitor combination with 5-lipoxygenase inhibitor for treatment of inflammation and inflammation-related disorders, compound preparation, antiarthritic activity and pharmaceutical compns.)

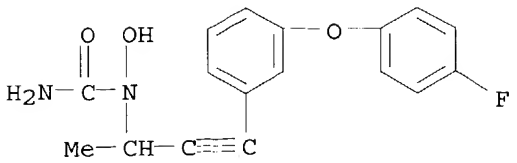
IT **187112-03-4**, A 72694 **187112-04-5**, A 80263
187112-09-0, Bay-q 1531 **187112-10-3**, BF 397
187112-11-4, BW 4C **187112-12-5**, BW 70C
187112-17-0, CHF 1909 **187112-22-7**, EF 40
187112-23-8, EN 105 187112-24-9, Floculide **187112-26-1**
, FPL 64170 **187112-28-3**, GR 80907 187112-29-4, HP 977
187112-30-7, HX 0386 **187112-32-9**, L 691816
187112-33-0, Linazolast **187112-35-2**, LY 280810
187112-36-3, MM 7002 **187112-41-0**, P 8892
187112-42-1, P 8977 **187112-43-2**, PD 136005
187112-44-3, PD 145246 **187112-50-1**, RU 46057
187112-51-2, RU 54808 **187112-52-3**, SL 81-0433
187112-54-5, SS 81OH 187112-56-7, Tanabe 757 187112-57-8,
Tanabe 799 **187112-58-9**, TMK 685 **187112-59-0**, TZI 2721
187112-62-5, WAY 125007 **187112-64-7**, ZD 7717
187112-65-8, ZM 216800 **193739-23-0**, CMI 392
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase-2 inhibitor combination with 5-lipoxygenase inhibitor for treatment of inflammation and inflammation-related disorders, compound preparation, antiarthritic activity and pharmaceutical compns.)

IT **455-91-4P 18931-60-7P 170570-77-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction; cyclooxygenase-2 inhibitor combination with 5-lipoxygenase inhibitor for treatment of inflammation and inflammation-related disorders, compound preparation, antiarthritic activity and pharmaceutical compns.)

IT **99-91-2**, 4'-Chloroacetophenone **321-28-8**, 2-Fluoroanisole
383-63-1, Ethyl trifluoroacetate **454-31-9**, Ethyl difluoroacetate **27918-19-0**, 4-Sulfonamidophenylhydrazine hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction; cyclooxygenase-2 inhibitor combination with 5-lipoxygenase inhibitor for treatment of inflammation and inflammation-related disorders, compound preparation, antiarthritic activity and pharmaceutical compns.)

IT **141579-54-6**, A 76745
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(A 76745; cyclooxygenase-2 inhibitor combination with 5-lipoxygenase inhibitor for treatment of inflammation and inflammation-related disorders, compound preparation, antiarthritic activity and pharmaceutical compns.)

RN 141579-54-6 HCAPLUS
CN Urea, N-[3-[3-(4-fluorophenoxy)phenyl]-1-methyl-2-propynyl]-N-hydroxy-
(9CI) (CA INDEX NAME)



IT **141579-54-6**, A 76745
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(A 76745; cyclooxygenase-2 inhibitor combination with 5-lipoxygenase inhibitor for treatment of inflammation and inflammation-related disorders, compound preparation, antiarthritic activity and pharmaceutical compns.)

IT **187112-47-6**, R 840 (Pharmaceutical)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(R 840; cyclooxygenase-2 inhibitor combination with 5-lipoxygenase inhibitor for treatment of inflammation and inflammation-related disorders, compound preparation, antiarthritic activity and pharmaceutical compns.)

IT **170569-86-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclooxygenase-2 inhibitor combination with 5-lipoxygenase inhibitor for treatment of inflammation and inflammation-related disorders, compound preparation, antiarthritic activity and pharmaceutical compns.)

IT **341-88-8**, KF-8940 **4737-26-2**, Isoflavan
27686-84-6, Masoprocol **34334-69-5**, Cirsiliol
36441-32-4, DuP-654 **46721-85-1**, CBS-1114
60284-71-1, AHR-5333 **71125-38-7**, Meloxicam
75139-38-7, Carbazomycin B **79916-77-1**, Forsythiaside
80809-81-0, Docebenone **87660-25-1**, ONO 5349
91431-42-4, Lonapalene **92532-05-3**, Rev 5367
93211-49-5, L-651392 **96314-49-7**, TEI-8005
96920-48-8, TMK 992 **96928-53-9**, TMK-919
99107-52-5, Bunaprolast **99134-29-9**, L-651896
99318-09-9, QA-208-199 **100035-75-4**, Evandamine
101335-99-3, Eprovafen **101618-31-9**, TMK 789
101619-08-3, TMK 781 **101619-11-8**, TMK-777
101910-24-1, PF-5901 **102612-16-8**, L-656224
103141-09-9, FPL 62064 **103475-41-8**, Tepoxalin
104007-80-9, TZI-41127 **104153-37-9**, Rilopirox
105357-17-3, SC-41661A **107008-29-7**, L-652343
107746-52-1, E 5110 **107889-32-7**, LY 178002
110033-17-5, WY 47288 **110406-33-2** **110545-79-4**,
SCH 40120 **111406-87-2**, Zileuton **111525-11-2**, A 63162
111908-94-2, SK&F-104351 **111908-95-3**, SK&F-104493
111974-60-8, Wy-48252 **112344-52-2**, Flobufen
114832-13-2, CGS-8515 **114917-95-2**, BMY-30094
115255-10-2, ONO-LP 219 **115255-23-7**, ONO-LP 269
115816-05-2, BI-L-93BS **117574-40-0**, CV-6504
118414-82-7, L 663536 **118420-47-6**, AL-3264
119256-94-9, FR 110302 **120164-49-0**, E-6080
120210-48-2, Tenidap **120602-97-3**, RG-6866
121135-51-1, 210-610 **121412-39-3**, CGS-21595
121502-05-4, PD-127443 **122454-69-7**, SK&F-105809
122610-85-9, A-65260 **123016-21-7**, Wy-50295
123606-23-5, A-69412 **123653-11-2**, NS-398

125721-82-6, BIL 226XX **125722-16-9**, Enofelast
127245-22-1, BF-389 **127378-46-5**, CI 987
127481-38-3, L-674636 **128253-31-6**, Bay-x-1005
129424-08-4, ICI-211965 **130116-16-4**, CI-986
130838-15-2, Y-19432 **131817-86-2**, CGS 22745
132392-65-5, LY-269415 **132734-43-1**, LY-233569
132956-22-0, Enazadrem phosphate **133174-26-2**, L-670630
133430-69-0, ETH-615 **134470-36-3**, BW-B 218C
134470-38-5, BW-B 70C **134822-78-9**, CGS-23885
134823-10-2, CGS 24891 **135133-84-5**, SC-45662
135872-69-4, WAY 120739 **135872-94-5**, WAY 121520
138331-04-1, R-68151 **139149-55-6**, SB-202235
139340-56-0, CI 1004 **140841-32-3**, ZD-2138
141579-67-1, A-78773 **141579-87-5**, A-79175
143964-80-1, F-1322 **145096-30-6**, E 3040
146935-39-9, Epocarbazolin A **147030-01-1**, MK-591
147317-96-2, Nitrosoxacin A **147497-10-7**, CGS 26529
147936-06-9, L-699333 **148915-76-8**, BU 4601A
149539-02-6, BI-L-357 **150693-65-5**, Lagunamycin
153950-29-9, A 121798 **154214-70-7**, R-85355
154355-76-7, ABT 761 **155944-23-3**, ZM 230487
156897-06-2, ML-3000 **158930-07-5**, L 739010
162011-90-7, MK 966 **169590-41-4** **177660-77-4**
177660-92-3 **181695-72-7** **185344-55-2**
187112-03-4, A 72694 **187112-04-5**, A 80263
187112-09-0, Bay-q 1531 **187112-10-3**, BF 397 **187112-11-4**, BW 4C **187112-12-5**, BW 70C **187112-17-0**, CHF 1909 **187112-22-7**, EF 40 **187112-23-8**, EN 105
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187112-30-7, HX 0386 **187112-32-9**, L 691816
187112-33-0, Linazolast **187112-35-2**, LY 280810
187112-36-3, MM 7002 **187112-41-0**, P 8892
187112-42-1, P 8977 **187112-43-2**, PD 136005
187112-44-3, PD 145246 **187112-50-1**, RU 46057
187112-52-3, SL 81-0433 **187112-54-5**, SS 81OH
187112-58-9, TMK 685 **187112-59-0**, TZI 2721
187112-62-5, WAY 125007 **187112-64-7**, ZD 7717
187112-65-8, ZM 216800 **193739-23-0**, CMI 392
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase-2 inhibitor combination with 5-lipoxygenase inhibitor for treatment of inflammation and inflammation-related disorders, compound preparation, antiarthritic activity and pharmaceutical compns.)

IT **455-91-4P** **18931-60-7P** **170570-77-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction; cyclooxygenase-2 inhibitor combination with 5-lipoxygenase inhibitor for treatment of inflammation and inflammation-related disorders, compound preparation, antiarthritic activity and pharmaceutical compns.)

IT **99-91-2**, 4'-Chloroacetophenone **321-28-8**, 2-Fluoroanisole **383-63-1**, Ethyl trifluoroacetate **454-31-9**, Ethyl difluoroacetate **27918-19-0**, 4-Sulfonamidophenylhydrazine hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction; cyclooxygenase-2 inhibitor combination with 5-lipoxygenase inhibitor for treatment of inflammation and inflammation-related disorders, compound preparation, antiarthritic activity and pharmaceutical compns.)

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 12:14:06 ON 30 JUL 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 30 Jul 2004 VOL 141 ISS 6
FILE LAST UPDATED: 29 Jul 2004 (20040729/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l100 not l199
L200 9 L100 NOT L199

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	[redacted]	[redacted]

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	[redacted]	[redacted]

FILE 'STNGUIDE' ENTERED AT 12:14:20 ON 30 JUL 2004
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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jul 23, 2004 (20040723/UP).

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L200 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:617977 HCAPLUS
DOCUMENT NUMBER: 127:257644
TITLE: **Combination** therapeutic methods employing nitric oxide scavengers and inhibitors of nitric oxide synthase-inducing species, and **compositions** useful therefor
INVENTOR(S): Lai, Ching-San
PATENT ASSIGNEE(S): Medinox, Inc., USA; Lai, Ching-San
SOURCE: PCT Int. Appl., 44 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9732585	A1	19970912	WO 1997-US4131	19970305 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2238029	AA	19970912	CA 1997-2238029	19970305 <--
AU 9722131	A1	19970922	AU 1997-22131	19970305 <--
JP 2000506170	T2	20000523	JP 1997-532042	19970305 <--
AU 9869984	A1	19980730	AU 1998-69984	19980609 <--
AU 722361	B2	20000803		

PRIORITY APPLN. INFO.:
US 1996-12820P P 19960305 <--
US 1995-561594 A 19951121 <--
WO 1997-US4131 W 19970305

OTHER SOURCE(S): MARPAT 127:257644

AB In accordance with the present invention, there are provided **combination** therapeutic methods for the in vivo inactivation or inhibition of formation (either directly or indirectly) of species which induce the expression of nitric oxide synthase, as well as reducing nitric oxide levels produced as a result of NO synthase expression. In contrast to the inhibitory approach described in the prior art (i.e., wherein the function of the enzymes responsible for nitric oxide production is inhibited), the present invention employs a **combination** of inactivation (or inhibition) and a scavenging approach whereby the stimulus of nitric oxide synthase expression is inactivated, or the production thereof is inhibited, and overproduced nitric oxide is bound in vivo to a suitable nitric oxide scavenger. The resulting complexes render the stimulus of nitric oxide synthase expression inactive (or inhibit the production thereof), and nitric oxide harmless. The resulting complexes are eventually excreted in the urine of the host. In another aspect, the present invention relates to reducing elevated nitric oxide levels associated with infectious and/or inflammatory conditions (and the treatment thereof), employing a **combination** therapeutic method wherein an agent for the treatment of the infectious and/or inflammatory condition is co-administered along with a dithiocarbamate compound as a scavenger of overproduced nitric oxide. Further in accordance with the present invention, there are provided **compns.** and formulations useful for carrying out the above-described methods.

IC ICM A61K031-495
ICS A61K031-44; A61K031-50; A61K038-00; A61K045-05; A01N043-58; A01N043-60; A01N043-42; C07K016-00; C12P021-08

CC 1-12 (Pharmacology)
Section cross-reference(s): 63

ST nitric oxide scavenger **combination** therapeutic; dithiocarbamate compd NO scavenger **combination** therapeutic; NO synthase inducer inhibitor **combination** therapeutic

IT Proteins, specific or class
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

(Uses)
(BPI (bactericidal/permeability-increasing); nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Intestine, disease
(Crohn's, therapeutic agents for; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Complement
(activation, inhibitors; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Interleukin 1 receptors
Platelet-activating factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonists; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Interleukin 6
Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antibodies to; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bradykinin receptor-blocking; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Ion channel blockers
(calcium, dihydropyridine; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Blood coagulation
(cascade, inhibitors; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Drug delivery systems
(emulsions; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Toxins
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(endotoxins; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Drug delivery systems
(enteric-coated; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Pancreatic islet of Langerhans
(free or encapsulated; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Drug delivery systems
(inhalants; nitric oxide scavengers with inhibitors of nitric oxide

synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Drug delivery systems
(injections, i.v.; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Drug delivery systems
(injections, s.c.; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(lipopolysaccharide-binding, antibodies to; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Drug delivery systems
(liposomes; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Drug delivery systems
(liqs., dispersions; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Drug delivery systems
(micelles; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal, OKT3; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Anti-inflammatory agents
Antidiabetic agents
Bacteria (Eubacteria)
Drug delivery systems
Immunosuppressants
Radical scavengers
(nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Blood-coagulation factors
Bradykinin receptors
Cytokine receptors
Cytokines
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Corticosteroids, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Interleukin 10
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Interleukin 13
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Interleukin 4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Prostaglandins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Leukotriene antagonists
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Drug delivery systems
(oral; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Drug delivery systems
(parenterals; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Drug delivery systems
(rectal; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT CD14 (antigen)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(soluble protein; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Tumor necrosis factor receptors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(soluble; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Drug delivery systems

(solids; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Drug delivery systems
(solns.; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Quaternary ammonium compounds, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tetraalkyl, with dithiocarbamate derivs.; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(to cytokines and other substances; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Complement receptors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(type 1, soluble; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Transforming growth factors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β-; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ, antibodies to; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT Interferon receptors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(γ-interferon, soluble; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT 9001-30-3, Blood-coagulation factor XII 80295-54-1, Complement C5a
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antibodies to; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT 9025-82-5, Phosphodiesterase 9029-60-1, **Lipoxygenase**
39391-18-9, **Cyclooxygenase** 57576-52-0, Thromboxane A2
80295-70-1, C1 Esterase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; nitric oxide scavengers with **inhibitors** of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT 506-32-1

RL: BSU (Biological study, unclassified); BIOL (Biological study) (metabolites; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT 140608-64-6, Muromonab CD3
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT 58-82-2, Bradykinin 65154-06-5, Blood platelet activating factor
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT 50-44-2, 6-Mercaptopurine 50-78-2, Aspirin 79-17-4, Aminoguanidine 89-57-6, Mesalamine 443-48-1, Metronidazole 446-86-6, Azathioprine 513-74-6D, Ammonium dithiocarbamate, derivs. 599-79-1, Sulfasalazine 867-44-7 1404-26-8, Polymyxin B 4384-81-0D, Sodium dithiocarbamate, derivs. 7439-89-6D, Iron, dithiocarbamate complexes, biological studies 7439-96-5D, Manganese, dithiocarbamate complexes, biological studies 7440-48-4D, Cobalt, dithiocarbamate complexes, biological studies 7440-50-8D, Copper, dithiocarbamate complexes, biological studies 9004-10-8, Insulin, biological studies 59865-13-3, **Cyclosporin** A 104987-11-3, FK506 106602-62-4, Amylin 160525-37-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT 10102-43-9, Nitric oxide, biological studies 125978-95-2, Nitric oxide synthase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

IT 594-07-0D, Dithiocarbamic acid, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide-scavenging; nitric oxide scavengers with inhibitors of nitric oxide synthase-inducing species for **combination** therapeutic methods and **compns.**)

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L200 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:450109 HCAPLUS
DOCUMENT NUMBER: 127:60628
TITLE: **Combination** therapeutic methods employing nitric oxide scavengers

INVENTOR(S): Lai, Ching-San
PATENT ASSIGNEE(S): Medinox, Inc., USA; Lai, Ching-San
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9718805	A1	19970529	WO 1996-US18124	19961112 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5747532	A	19980505	US 1995-561594	19951121 <--
CA 2238028	AA	19970529	CA 1996-2238028	19961112 <--
AU 9676784	A1	19970611	AU 1996-76784	19961112 <--
EP 866695	A1	19980930	EP 1996-939670	19961112 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1202824	A	19981223	CN 1996-198435	19961112 <--
CN 1096855	B	20021225		
JP 2000500493	T2	20000118	JP 1997-519776	19961112 <--
TW 516957	B	20030111	TW 1996-85114207	19961119 <--
AU 9869984	A1	19980730	AU 1998-69984	19980609 <--
AU 722361	B2	20000803		

PRIORITY APPLN. INFO.: US 1995-561594 A2 19951121 <--
US 1996-12820P P 19960305 <--
WO 1996-US18124 W 19961112 <--

OTHER SOURCE(S): MARPAT 127:60628

AB **Combination** therapeutic methods are provided for the in vivo inactivation or inhibition of formation (either directly or indirectly) of species which induce the expression of nitric oxide synthase, as well as reducing nitric oxide levels produced as a result of NO synthase expression. In contrast to the inhibitory approach described in the prior art (i.e., wherein the function of the enzymes responsible for nitric oxide production is inhibited), the present invention employs a **combination** of inactivation (or inhibition) and scavenging approaches, whereby the stimulus of nitric oxide synthase expression is inactivated, or the production thereof is inhibited, and overproduced nitric oxide is bound in vivo to a suitable nitric oxide scavenger. The resulting complexes render the stimulus of nitric oxide synthase expression inactive (or inhibit the production thereof), and nitric oxide harmless. The resulting complexes are eventually excreted in the urine of the host. Also provided are **compns.** and formulations useful for carrying out the above methods.

IC ICM A61K031-325

CC 1-12 (Pharmacology)
Section cross-reference(s): 63

ST NO synthase inhibitor **combination** therapeutic; nitric oxide scavenger **combination** therapeutic

IT Proteins, specific or class
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

(Uses)
(BPI (bactericidal/permeability-increasing); nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Intestine, disease
(Crohn's, therapeutic agents for; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Complement
(activation, inhibitors; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Transplant and Transplantation
Transplant and Transplantation
(allotransplant, heart; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Heart
Heart
(allotransplant; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Interleukin 1 receptors
Platelet-activating factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonists; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Interleukin 6
Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antibodies to; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Tear (ocular fluid)
(artificial; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Ion channel blockers
Ion channel blockers
(calcium, dihydropyridine; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Drug delivery systems
(drops; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Drug delivery systems
(emulsions; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Toxins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(endotoxins; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Drug delivery systems
(inhalants; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Drug delivery systems
(injections, i.v.; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Drug delivery systems
(injections, s.c.; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Proteins, specific or class
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(iron-containing; nitric oxide-scavenging and nitric oxide

synthase-inhibiting **combinations** for therapeutic use)

IT Proteins, specific or class
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lipopolysaccharide-binding, soluble; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Drug delivery systems
(liposomes; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Drug delivery systems
(liqs., dispersions; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal, OKT3; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Anti-inflammatory agents
Anticoagulants
Antidiabetic agents
Antihypotensives
Bacteria (Eubacteria)
Drug delivery systems
Drugs
Immunosuppressants
Pancreatic islet of Langerhans
Scavengers
Transplant rejection
(nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Antibiotics
Antibodies
Corticosteroids, biological studies
Interleukin 10
Interleukin 13
Interleukin 4
Metalloporphyrins
Porphyrins
Prostaglandins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Blood-coagulation factors
Bradykinin receptors
Cytokine receptors
Cytokines
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Leukotriene antagonists
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(non-heme iron-containing; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Drug delivery systems
(ophthalmic; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Drug delivery systems
(oral; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Drug delivery systems
(parenterals; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Drug delivery systems
(rectal; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Shock (circulatory collapse)
(septic; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT CD14 (antigen)
Tumor necrosis factor receptors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(soluble; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Drug delivery systems
(solids; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Drug delivery systems
(solns.; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Eye, disease
(therapeutic agents for; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Globulins, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thymoglobulin; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Complement receptors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(type 1, soluble; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Transition metal complexes
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(with dithiocarbamates; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Transforming growth factors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β-; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Interferons

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ, antibodies to; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT Interferon receptors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(γ-interferon, soluble; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT 9001-30-3, Blood coagulation factor XII 80295-54-1, Complement C5a
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antibodies to; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT 9025-82-5, Phosphodiesterase 9029-60-1, **Lipoxygenase** 39391-18-9, **Cyclooxygenase** 57576-52-0, Thromboxane A2 80295-70-1, C1 Esterase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; nitric oxide-scavenging and nitric oxide synthase-**inhibiting combinations** for therapeutic use)

IT 506-32-1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabolites; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT 140608-64-6, Muromonab CD3
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT 50-02-2 50-24-8, Prednisolone 50-33-9, Phenylbutazone, biological studies 50-44-2, 6-Mercaptopurine 50-78-2, Aspirin 53-86-1, Indomethacin 59-66-5, Acetazolamide 70-51-9, Desferrioxamine 79-17-4, Aminoguanidine 83-43-2, Methylprednisolone 89-57-6, Mesalamine 92-13-7, Pilocarpine 443-48-1, Metronidazole 446-86-6, Azathioprine 512-15-2, Cyclopentolate 594-07-0D, Dithiocarbamic acid, dithiocarbamates 599-79-1, Sulfasalazine 737-86-0, Pyridoxal isonicotinoyl hydrazone 867-44-7 1404-26-8, Polymyxin B 2418-14-6, Dimercaptosuccinic acid 4428-95-9, Foscarnet 7439-89-6D, Iron, dithiocarbamate complexes, biological studies 7439-96-5D, Manganese, dithiocarbamate complexes, biological studies 7440-48-4D, Cobalt, dithiocarbamate complexes, biological studies 7440-50-8D, Copper, dithiocarbamate complexes, biological studies 9004-10-8, Insulin, biological studies 12678-01-2, Phenanthroline 22664-55-7, Metipranolol 24280-93-1, Mycophenolic acid 24584-09-6, ICRF-187 26839-75-8, Timolol 30652-11-0, 1,2-Dimethyl-3-hydroxypyrid-4-one 47141-42-4, Levobunolol 53774-63-3 53882-12-5, Lodoxamide 73384-59-5, Ceftriaxone 79217-60-0, **Cyclosporin** 82410-32-0, Ganciclovir 94161-07-6, N-Methyl-D-glucamine dithiocarbamate 94161-07-6D, N-Methyl-D-glucamine dithiocarbamate, iron complexes 104987-11-3, FK506 106602-62-4, Amylin 160525-37-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT 58-82-2, Bradykinin 10102-43-9, Nitric oxide, biological studies 65154-06-5, Platelet-activating factor 125978-95-2, Nitric oxide synthase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

IT 69-72-7, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(salicylates; nitric oxide-scavenging and nitric oxide synthase-inhibiting **combinations** for therapeutic use)

L200 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:727025 HCAPLUS
DOCUMENT NUMBER: 126:112898
TITLE: The NF-κB inhibitor, tepoxalin, suppresses surface expression of the cell adhesion molecules CD62E, CD11b/CD18 and CD106
AUTHOR(S): Lee, Daniel H. S.; Tam, Susanna S. C.; Wang, Elizabeth; Taylor, Gareth R.; Plante, Richard K.; Lau, Catherine Y.
CORPORATE SOURCE: The R.W. Johnson Pharmaceutical Research Institute, 19 Green Belt Drive, Don Mills, Ontario, M3C 1L9, Can.
SOURCE: Immunology Letters (**1996**), 53(2,3), 109-113
CODEN: IMLED6; ISSN: 0165-2478
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tepoxalin, a **dual** enzyme **inhibitor** of **cyclooxygenase** and **5-lipoxygenase** has been shown to **inhibit** T-cell activation. Its immunosuppressive property is distinct from **cyclosporin** because only tepoxalin, but not **cyclosporin**, suppresses NF-κB activation. Here the authors report that tepoxalin selectively inhibits intercellular adhesion mol.-1 (ICAM-1, CD54)/MAC-1 (CD11b/CD18) dependent adhesion of polymorphonuclear cells to IL-1 activated human umbilical vein endothelial cells. The mechanism of inhibition is related to the surface expression of several cell adhesion mols. Flow cytometry analyses on cultured cells that were treated with tepoxalin or antisense oligonucleotides to the p65/p50 subunit of NF-.vkappa.B, and then stimulated with PMA, revealed a reduced expression of CD11b/CD18 on monocytic HL60 cells, and endothelial adhesion mol.-1 (CD62E) and vascular adhesion mol.-1 (CD106) on human umbilical vein endothelial cells. Expression of other adhesion mols. such as lymphocyte function associated-antigen-1 (CD11a/CD18) and CD54 were unaffected. Tepoxalin also inhibited the secretion of a NF-.vkappa.B regulated chemokine, IL-8, a known inducer of CD11b/CD18 expression. Thus the suppression of CD11b/CD18 expression by tepoxalin may involve IL-8. The results suggest that by inhibiting NF-.vkappa.B activation, surface expression of several adhesion mols. can be modulated and that tepoxalin may be useful in treating selected adhesion mediated events such as leukocyte migration or atherosclerotic plaque formation.

CC 1-7 (Pharmacology)
IT Polymorphonuclear **leukocyte**
(NF-κB inhibitor tepoxalin suppresses surface expression of cell adhesion mols. CD62E and CD11b/CD18 and CD106 in relation to inhibition of polymorphonuclear cells to vascular endothelium and IL-8 secretion)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L200 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:865559 HCAPLUS
DOCUMENT NUMBER: 123:306186
TITLE: Tepoxalin, a novel immunomodulatory compound,

synergizes with CSA in suppression of graft-versus-host reaction and allogeneic skin graft rejection

AUTHOR(S): Fung-Leung, Wai-Ping; Pope, Barbara L.; Chourmouzis, Erika; Panakos, Julie A.; Lau, Catherine Y.

CORPORATE SOURCE: R.W. Johnson Pharmaceutical Research Institute, Don Mills, ON, M3C 1L9, Can.

SOURCE: Transplantation (**1995**), 60(4), 362-8
CODEN: TRPLAU; ISSN: 0041-1337

PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tepoxalin, a **dual** 5-**lipoxygenase** and **cyclooxygenase inhibitor** with nonsteroidal antiinflammatory effects, has recently been shown to suppress NFκB transactivation and **inhibit** T cell proliferation via a mechanism very different from **cyclosporine** (CsA). In this report, we demonstrate that this novel immunosuppressive effect of tepoxalin is manifested in in vivo transplantation models. Tepoxalin suppressed murine spleen cell proliferation in a **mixed** lymphocyte reaction (MLR) with an IC50 of 1.3 μM. Coadministration of tepoxalin and CsA in MLR cultures showed an additive **inhibitory** effect. Oral administration of tepoxalin at 12 mg/kg/day to mice suppressed local graft-vs.-host (GVH) responses by about 40% (n=10). **Combination** of tepoxalin and CsA at suboptimal doses **synergized** their immunosuppressive effects on GVH responses (n=20). In skin transplantation, the median survival time of allogeneic BALB/cByJ (H-2d) mouse skin grafted onto C3H/HeJ (H-2k) mice was 10.5 days (n=8), and was prolonged to 15.0 days (n=9) for recipient mice administered tepoxalin at 50 mg/kg/day. Coadministration of suboptimal doses of tepoxalin (12.5 mg/kg/day) and CsA (50 mg/kg/day) prolonged skin graft rejections dramatically (55% of the grafts survived for more than 40 days, n=9). Taken together, these results demonstrate that tepoxalin is a potent immunomodulatory compound that, when **combined** with CsA, provides **synergistic** immunosuppressive activity. The fact that tepoxalin and CsA act on different transcription factors, NFκB and NFAT resp., might explain the **synergistic** suppressive effects when both compds. were used. Tepoxalin could be an important addition to the cohort of immunosuppressive therapies currently used in solid organ and bone marrow transplantations.

CC 1-7 (Pharmacology)

ST tepoxalin **synergism cyclosporine** immunosuppressant transplantation

IT **Immunosuppressants**
Lymphocyte
Transplant and Transplantation
(tepoxalin **synergistic** interaction with **cyclosporine** as immunosuppressants in graft-vs.-host reaction and allogeneic skin graft rejection)

IT Drug interactions
(**synergistic**, tepoxalin **synergistic** interaction with **cyclosporine** as immunosuppressants in graft-vs.-host reaction and allogeneic skin graft rejection)

IT 59865-13-3, **Cyclosporin** A 103475-41-8, Tepoxalin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tepoxalin **synergistic** interaction with **cyclosporine** as immunosuppressants in graft-vs.-host reaction and allogeneic skin graft rejection)

L200 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:260855 HCAPLUS
DOCUMENT NUMBER: 120:260855
TITLE: α-Tocopherol prevents **cyclosporin** A-mediated activation of phospholipase A2 and inhibition of Na+, K+-ATPase activity in cultured hamster renal tubular cells
AUTHOR(S): Anderson, Ronald; Van Rensburg, Constance E. J.; Myer, Martin S.
CORPORATE SOURCE: Inst. Pathol., Univ. Pretoria, Pretoria, 0001, S. Afr.
SOURCE: Toxicology and Applied Pharmacology (**1994**), 125(2), 176-83
CODEN: TXAPA9; ISSN: 0041-008X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB At concns. of 0.5 μM and upward, **cyclosporin** A (CsA) caused dose-related **inhibition** of the growth of a hamster renal tubular cell line (HAK ATCC; CCL15) in vitro. **Inhibition** of cell growth was due to the cytotoxic properties of CsA which were associated with enhancement of activity of phospholipase A2 (PLA2) according to the increased generation of arachidonic acid and lysophosphatidylcholine (LPC). Arachidonate per se, at concns. of up to 20 μM, did not affect the growth of HAK cells, while **cyclooxygenase** and **5-lipoxygenase inhibitors** failed to protect the cells against the antiproliferative effects of CsA. However, LPC caused dose-related **inhibition** of the growth of HAK cells. Moreover, coincubation with lysophospholipase or α-tocopherol (AT, vitamin E), a PLA2 **inhibitory** and lysophospholipid-complexing agent, protected the HAK cells against both CSA and LPC. The Na+, K+-ATPase activity of Hak cells was also **inhibited** by CsA, with the enzyme being protected by inclusion of AT or lysophospholipase. Increased activity of PLA2 and **inhibition** of Na+, K+-ATPase preceded cytotoxicity and cytolysis. Excessive production of lysophospholipids and consequent **inhibition** of Na+, K+-ATPase in renal tubular cells is a possible mechanism of CsA-induced nephrotoxicity. The protective effects of AT suggest that this agent may be clin. useful in preventing the renal side effects of CsA.

CC 1-7 (Pharmacology)
ST tocopherol **cyclosporine** phospholipase A2 ATPase nephrotoxicity
IT Kidney, toxic chemical and physical damage
(**cyclosporin** A toxicity to, potassium-sodium-dependent ATPase and phospholipase A2 change in, α-tocopherol prevention of)
IT Kidney, **composition**
(potassium-sodium-dependent ATPase and phospholipase A2 of, **cyclosporin** A-mediated change in, α-tocopherol prevention of)
IT 9001-84-7, Phospholipase A2
RL: BIOL (Biological study)
(**cyclosporin** A-mediated activation of kidney, α-tocopherol prevention of)
IT 58-95-7, α-Tocopherol acetate 59-02-9, α-Tocopherol
9001-85-8, Lysophospholipase
RL: BIOL (Biological study)
(**cyclosporin** A-mediated activation of phospholipase A2 and inhibition of sodium, potassium-ATPase in kidney prevention by)
IT 59865-13-3, **Cyclosporin** A
RL: BIOL (Biological study)
(phospholipase A2 activation and sodium, potassium-ATPase inhibition in kidney mediation by, α-tocopherol prevention of)

IT 9000-83-3, ATPase
RL: BIOL (Biological study)
(potassium-sodium-dependent, **cyclosporin** A-mediated inhibition of kidney, α-tocopherol prevention of)

L200 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:332 HCAPLUS
DOCUMENT NUMBER: 114:332
TITLE: Comparative actions of immunosuppressants, glucocorticoids and nonsteroidal anti-inflammatory drugs on various models of delayed hypersensitivity and on a nonimmune inflammation in mice
AUTHOR(S): Tarayre, J. P.; Barbara, M.; Aliaga, M.; Tisne-Versailles, J.
CORPORATE SOURCE: Dep. Pharmacol., P. Fabre Res. Cent., Castres, F-81106, Fr.
SOURCE: Arzneimittel-Forschung (**1990**), 40(10), 1125-31
CODEN: ARZNAD; ISSN: 0004-4172
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Various models of delayed hypersensitivity (DH) were used in mice: contact hypersensitivity reactions to picryl chloride and oxazolone and reactions to methylated bovine serum albumin (MBSA) and sheep red blood cells (SRBC). Drugs of different classes were tested in these models by systemic treatment around the challenge period: non-steroidal anti-inflammatory drugs (**cyclooxygenase inhibitors**, and **inhibitors** of both **cyclooxygenase** and **lipoxygenase**); glucocorticoids and immunosuppressants (**cyclosporin** A, CsA; cyclophosphamide, Cy; methotrexate, Mtx; azathioprine, Aza). These compds. were also studied and compared for their effects on the 3-h and 24-h phase of the carrageenin mouse-paw edema (in which inflammation is maximal after 24 h). Non-steroidal anti-inflammatory drugs (including double **inhibitors** of **cyclooxygenase** and **lipoxygenase**) had little or no effect on DH models, except indomethacin. Glucocorticoids **inhibited** all immune reactions except that to MBSA. Of the immunosuppressants, CsA reduced all the DH reactions while Aza mainly reduced the reaction to SRBC; Cy and Mtx were mainly active on SRBC and MBSA inflammations. On the other hand CsA, Cy, and Mtx were inactive on the 3-h phase but decreased the 24-h phase of carrageenin edema. At doses active on the DH models and on carrageenin inflammation, Cy induced a lasting blood leukopenia, but CsA and Mtx did not. This **combination** of tests in the mouse seems to be of interest to demonstrate any action on DH and any antiinflammatory effect and to suggest whether these activities are related to a possible leukopenia effect. CsA and Mtx, which reduced DH reactions with anti-inflammatory effect on the 24-h phase of the carrageenin-induced edema without major leukopenia action, appeared the most interesting immunosuppressants in these tests.
CC 1-7 (Pharmacology)
Section cross-reference(s): 2
IT 50-03-3, Hydrocortisone acetate 50-18-0, Cyclophosphamide 50-33-9, Phenylbutazone, biological studies 50-78-2 52-21-1, Prednisolone acetate 53-86-1, Indomethacin 59-05-2, Methotrexate 92-43-3, Phenidone 124-94-7, Triamcinolone 360-63-4, Betamethasone phosphate 446-86-6, Azathioprine 638-94-8, Desonide 1177-87-3, Dexamethasone acetate 5104-49-4, Flurbiprofen 22204-53-1, Naproxen 36322-90-4, Piroxicam 59865-13-3, **Cyclosporin** A 66000-40-6
RL: BIOL (Biological study)
(delayed hypersensitivity and nonimmune inflammation response to)

L200 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:53482 HCAPLUS
DOCUMENT NUMBER: 112:53482
TITLE: Potent inhibition of interleukin 1β-mediated human melanoma (A375.6) lysis by corticosteroids, staurosporine, and tilorone
AUTHOR(S): Schultz, Richard M.; Howbert, J. Jeffry; Archer, Robert A.
CORPORATE SOURCE: Dep. Immunol. Res. Chem., Cancer, Virol. Res., Lilly Corp. Cent., Indianapolis, IN, 46285, USA
SOURCE: Immunopharmacology and Immunotoxicology (**1989**), 11(2-3), 489-506
CODEN: IITOEF; ISSN: 0892-3973
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mechanism of human interleukin (IL)-1β-mediated cytolysis was studied in a human melanoma cell line, A375.6. Purified **recombinant** human IL-1β produced 50% cytocidal activity at 50 pg/mL. A variety of compds. were tested for their ability to interfere with A375.6 lysis. Compds. were added simultaneously with IL-1β (100 pg/mL), and tumor cytolysis was measured after 72 h of culture by release of 125I from DNA of A375.6 cells labeled with [125I]-dUrd. A variety of anti-inflammatory/immunosuppressive agents (including auranofin, chloroquine, **cyclosporin** A, d-penicillamine) and several **cyclooxygenase/lipoxygenase inhibitors** (AA-861, BW755c, and indomethacin) lacked protective activity. Similarly, phospholipase **inhibitors** (mepacrine and 4-bromophenacyl bromide), putrescine, **inhibitors** of lysosomal activity (chloroquine and NH4Cl), Ca channel **blockers** (nifedipine and verapamil), calmodulin **inhibitors** (W-7 and calmidazolium), and **inhibitors** of ADP ribosylation (nicotinamide and 3-aminobenzamide) were inactive. In contrast, corticosteroids (dexamethasone, hydrocortisone, and paramethasone acetate), tilorone, and protein kinase C **inhibitors** (1-[5-isoquinolinyl-sulfonyl]-2-methylpiperazine and staurosporine) **inhibited** IL-1β-mediated A375.6 cytolysis. These compds. also interfered with tumor necrosis factor-mediated lysis of A375.6, suggesting common mechanisms of tumor cytotoxicity by these monokines. This model may be useful for delineating intracellular biochem. events integral to IL-1 action.
CC 15-5 (Immunochemistry)

L200 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1989:433265 HCAPLUS
DOCUMENT NUMBER: 111:33265
TITLE: Effects of anti-inflammatory drugs on interleukin 1-induced cartilage proteoglycan resorption in vitro: inhibition by aurothiophosphines but no influence from perturbed eicosanoid metabolism
AUTHOR(S): Rainsford, K. D.
CORPORATE SOURCE: Anti-Inflammatory Res. Unit, Strangeways Res. Lab., Cambridge, CB1 4RN, UK
SOURCE: Journal of Pharmacy and Pharmacology (**1989**), 41(2), 112-17
CODEN: JPPMAB; ISSN: 0022-3573
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A range of anti-inflammatory drugs having varying effects on eicosanoid metabolism and other actions was studied for their potential to **inhibit** α-interleukin I (IL-1)-induced cartilage

proteoglycan resorption in vitro. No effects on resorption were observed with **inhibitors** of **cyclooxygenase** or **lipoxygense** or **mixed inhibitors** of both these enzymes, and no influence on IL-1 effects was observed with added eicosanoids. Among the clin. used disease-modifying antiarthritic agents, only auranofin and the immunoregulatory agent tilomisole were effective in **inhibiting** resorption. Some auranofin analogs having Cl or NO2 leaving groups that **inhibit** DNA polymerase-α were potent **inhibitors** of IL-1 induced resorption.

CC 1-7 (Pharmacology)

IT 9001-84-7, Phospholipase A2 39391-18-9, **Cyclooxygenase** 80619-02-9, 5-**Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**, resorption of proteoglycans of cartilage response to)

IT 50-18-0, Cyclophosphamide 50-44-2, 6-Mercaptopurine 51-17-2, 1H-Benzimidazole 52-67-5, D-Penicillamine 59-05-2, Methotrexate 70-49-5, Thiomalic acid 89-57-6, 5-Aminosalicylic acid 144-83-2, Sulfapyridine 446-86-6, Azathioprine 599-79-1, Sulfasalazine 1113-41-3, L-Penicillamine 4517-99-1 12244-57-4, Sodium aurothiomalate 14769-73-4, Levamisole 15529-90-5 18840-45-4 20902-45-8, Penicillamine disulfide 21256-18-8, Oxaprozin 22071-15-4, Ketoprofen 22494-27-5, Flufenisal 22494-47-9, Clobuzarit 30544-47-9, Etofenamate 34031-32-8, Auranofin 42924-53-8, Nabumetone 51579-82-9, Amfenac 57067-46-6 58433-11-7, Tilomisole 58456-91-0, MK-447 59804-37-4, Tenoxicam 59865-13-3, **Cyclosporin** A 60940-34-3, Ebselen 66000-40-6, BW-755c 71474-64-1 72105-94-3 74765-78-9 75060-92-3, ONO-3144 77167-93-2 78712-43-3, OKY-046 83533-66-8 99134-29-9 100944-16-9, Wy 45637 101910-24-1, REV-5901 110033-10-8, Wy 46905 112230-08-7, Wy 46679 121367-35-9, Wy 46904 121397-54-4, SKF 199336
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(resorption of proteoglycans of cartilage response to)

L200 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1987:508982 HCAPLUS
DOCUMENT NUMBER: 107:108982
TITLE: Improved rat cardiac allograft survival with nonsteroidal pharmacologic agents relate eicosanoids
AUTHOR(S): Foegh, M. L.; Khirabadi, B. S.; Ramwell,
CORPORATE SOURCE: Med. Cent., Georgetown Univ., Washington, USA
SOURCE: Transplantation Proceedings (**1987**), 19(1, Book 2), 1297-300
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **combination** of **cyclosporin** A (CsA, 0.5 mg/kg/day i.m.) or azathioprine (Aza, 5 mg/kg/day i.p.) with (1) prednisolone, prolongs allograft survival; (2) with **cyclooxygenase inhibitors** like indomethacin, does not prolong allograft survival; (3) with thromboxane antagonists and thromboxane synthase **inhibitors**, prolongs allograft survival; (4) with **5-lipoxygenase inhibitors**, prolongs allograft survival; and (5) with an LTD4 receptor antagonist it does not prolong allograft survival. Both **combinations** 3 and 4 prolong allograft survival to the same extent as the clin. used **combination** of CsA and Aza with prednisone.

CC 1-7 (Pharmacology)

ST heart allograft **cyclosporine** azathioprine eicosanoid
IT Eicosanoids
RL: BIOL (Biological study)
(heart allograft survival response to azathioprine and **cyclosporin** A and)
IT Thromboxanes
RL: BIOL (Biological study)
(receptors for, antagonists of, heart allograft survival response to **cyclosporin** A and azathioprine and)
IT Transplant and Transplantation, animal
(allo-, of heart, azathioprine and **cyclosporin** A and eicosanoid-related agents effect on)
IT Heart
(allotransplant, survival of, azathioprine and **cyclosporin** A and eicosanoid-related agents effect on)
IT 58-32-2, Dipyridamole 35121-78-9 78919-13-8, Iloprost 81443-73-4, AH23848
RL: BIOL (Biological study)
(heart allograft survival response to **cyclosporin** A and)
IT 50-24-8, Prednisolone 77167-93-2 80619-02-9 110120-68-8
RL: BIOL (Biological study)
(heart allograft survival response to **cyclosporin** A and azathioprine and)
IT 446-86-6 59865-13-3, **Cyclosporine** A
RL: BIOL (Biological study)
(heart allograft survival response to, eicosanoid-related agents in relation to)
IT 39391-18-9, **Cyclooxygenase** 61276-89-9, Thromboxane synthase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitor**, heart allograft survival response to azathioprine and)
IT 62168-75-6
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor, heart allograft survival response to **cyclosporin** A and azathioprine and)

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FULL ESTIMATED COST	[redacted]	[redacted]

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	[redacted]	[redacted]

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FULL ESTIMATED COST	[redacted]	[redacted]

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L201 ANSWER 1 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:199861 HCAPLUS
DOCUMENT NUMBER: 140:296705
TITLE: Licofelone-clinical update on a novel LOX/COX inhibitor for the treatment of osteoarthritis
AUTHOR(S): Alvaro-Gracia, J. M.
CORPORATE SOURCE: Servicio de Reumatologia, Hospital de la Princesa, Madrid, Spain
SOURCE: Rheumatology (Oxford, United Kingdom) (2004), 43(Suppl. 1), i21-i25
CODEN: RUMAFK; ISSN: 1462-0324
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Licofelone, a competitive **inhibitor** of 5-**lipoxygenase**, **cyclooxygenase** (COX)-1 and COX-2, is currently in clin. development for the treatment of osteoarthritis (OA). Licofelone decreases the production of proinflammatory leukotrienes and prostaglandins-which are involved in the pathophysiol. of OA and in gastrointestinal (GI) damage induced by NSAIDs- and has the potential to **combine** good analgesic and anti-inflammatory effects with excellent GI tolerability. Initial endoscopy data in healthy volunteers have demonstrated that licofelone is well tolerated and has a GI safety profile similar to placebo and significantly better than naproxen. These tolerability results were confirmed in patients with OA in two sep. randomized studies. Furthermore, a long-term study (52 wk) has shown that

licofelone is at least as effective as naproxen in the treatment of OA. Licofelone also appears to be as effective as the selective COX-2 inhibitor celecoxib in the treatment of the signs and symptoms of OA. Licofelone has a GI safety profile similar to that of celecoxib, but may offer the advantage of fewer incidences or worsening of peripheral edema. Preliminary data have also shown that licofelone coadministration with low-dose aspirin does not lead to increased GI toxicity. The emerging clin. data for licofelone indicate that it is an effective and well-tolerated therapy that could offer safety advantages over current treatment options, and that it could be suitable for the long-term treatment of a broad spectrum of patients with OA.

CC 1-0 (Pharmacology)

IT Analgesics
Anti-inflammatory agents
Human
Osteoarthritis
(LOX/COX inhibitor licofelone for treatment of patients with osteoarthritis)

IT **Antiarthritics**
(osteoarthritis; LOX/COX inhibitor licofelone for treatment of patients with osteoarthritis)

IT **80619-02-9**, **5-Lipoxygenase** 329900-75-6, **Cyclooxygenase**-2 329967-85-3, **Cyclooxygenase**-1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitor**; LOX/COX **inhibitor** licofelone for treatment of patients with osteoarthritis)

IT **80619-02-9**, **5-Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitor**; LOX/COX **inhibitor** licofelone for treatment of patients with osteoarthritis)

RN 80619-02-9 HCAPLUS

CN Oxygenase, arachidonate 5-lip- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **80619-02-9**, **5-Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitor**; LOX/COX **inhibitor** licofelone for treatment of patients with osteoarthritis)

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L201 ANSWER 2 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:785798 HCAPLUS
DOCUMENT NUMBER: 139:332141
TITLE: Licofelone Merckle
AUTHOR(S): Ding, Changhai; Cicuttini, Flavia
CORPORATE SOURCE: Menzies Centre for Population Health Research, University of Tasmania, Hobart, Tasmania, 7000, Australia
SOURCE: IDrugs (2003), 6(8), 802-808
CODEN: IDRUFN; ISSN: 1369-7056
PUBLISHER: Current Drugs
DOCUMENT TYPE: Journal; **General Review**

LANGUAGE: English
AB A review. EuroAlliance (a consortium of Alfa Wassermann SpA, Lacer SA and Merckle GmbH) is developing licofelone, a **dual cyclooxygenase** and **5-lipoxygenase inhibitor** for the potential treatment of inflammatory disorders including osteoarthritis.
CC 1-0 (Pharmacology)
IT Analgesics
Human
Inflammation
Osteoarthritis
(licofelone for treatment of patients with inflammation, pain, and osteoarthritis)
IT **Anti-inflammatory agents**
(nonsteroidal; licofelone for treatment of patients with inflammation, pain, and osteoarthritis)
IT **Antiarthritics**
(osteoarthritis; licofelone for treatment of patients with inflammation, pain, and osteoarthritis)
IT **80619-02-9, 5-Lipoxygenase** 329900-75-6, **Cyclooxygenase** 2 329967-85-3, **Cyclooxygenase** 1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitor**; licofelone for treatment of patients with inflammation, pain, and osteoarthritis)
IT **80619-02-9, 5-Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitor**; licofelone for treatment of patients with inflammation, pain, and osteoarthritis)
RN 80619-02-9 HCAPLUS
CN Oxygenase, arachidonate 5-lip- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **80619-02-9, 5-Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitor**; licofelone for treatment of patients with inflammation, pain, and osteoarthritis)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L201 ANSWER 3 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:645217 HCAPLUS
DOCUMENT NUMBER: 139:374015
TITLE: **Dual inhibition** of **cyclooxygenase**-2 (COX-2) and 5-lipoxygenase (5-LOX) as a new strategy to provide safer non-steroidal anti-inflammatory drugs
AUTHOR(S): Charlier, Caroline; Michaux, Catherine
CORPORATE SOURCE: Lab. de Chimie Moleculaire Structurale, Facultes Universitaires N.-D. de la Paix, Namur, B-5000, Belg.
SOURCE: European Journal of Medicinal Chemistry (2003), 38(7-8), 645-659
CODEN: EJMCA5; ISSN: 0223-5234
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. **Dual** COX/5-LOX (**cyclooxygenase/5-lipoxygenase**) **inhibitors** constitute a valuable alternative to classical non-steroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors for the treatment of inflammatory diseases. Indeed, these latter present diverse side effects, which are reduced or

absent in **dual**-acting agents. In this review, COX and 5-LOX pathways are first described to highlight the therapeutic interest of designing such compds. Various structural families of **dual** inhibitors are illustrated.

CC 1-0 (Pharmacology)

ST review **cyclooxygenase** 2 lipoxygenase **inhibitor** antiinflammatory

IT **Inflammation**
(**dual inhibition** of **cyclooxygenase**-2 and **5-lipoxygenase** as a new strategy to provide safer non-steroidal anti-inflammatory drugs)

IT **Anti-inflammatory agents**
(nonsteroidal; **dual inhibition** of **cyclooxygenase**-2 and **5-lipoxygenase** as a new strategy to provide safer non-steroidal anti-inflammatory drugs)

IT **80619-02-9, 5-Lipoxygenase** 329900-75-6, **Cyclooxygenase**-2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**dual inhibition** of **cyclooxygenase**-2 and **5-lipoxygenase** as a new strategy to provide safer non-steroidal anti-inflammatory drugs)

IT **80619-02-9, 5-Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**dual inhibition** of **cyclooxygenase**-2 and **5-lipoxygenase** as a new strategy to provide safer non-steroidal anti-inflammatory drugs)

RN 80619-02-9 HCAPLUS

CN Oxygenase, arachidonate 5-lip- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **80619-02-9, 5-Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**dual inhibition** of **cyclooxygenase**-2 and **5-lipoxygenase** as a new strategy to provide safer non-steroidal anti-inflammatory drugs)

REFERENCE COUNT: 136 THERE ARE 136 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L201 ANSWER 4 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:500329 HCAPLUS

DOCUMENT NUMBER: 139:373941

TITLE: COX-LOX inhibition: Current evidence for an emerging new therapy

AUTHOR(S): Skelly, M. M.; Hawkey, C. J.

CORPORATE SOURCE: Division of Gastroenterology, Queen's Medical Centre, University Hospital, Nottingham, UK

SOURCE: International Journal of Clinical Practice (2003), 57(4), 301-304
CODEN: IJCPF9; ISSN: 1368-5031

PUBLISHER: Medicom International

DOCUMENT TYPE: Journal; **General Review**

LANGUAGE: English

AB A review. Safe and effective drug treatment is an important objective of all doctors. In the treatment of arthritis, non-steroidal anti-inflammatory drugs offer effective treatment but safety is significantly limited, largely due to gastrointestinal toxicity. Attention has recently focused on exploiting increased knowledge of metabolism of arachidonic acid to allow the development of safer anti-inflammatory drugs. **Dual** inhibitors of cyclo-oxygenase and lipoxygenase are

planned. These drugs may inhibit formation of both prostaglandins and leukotrienes. This review outlines the salient features of cyclo-oxygenase and lipoxygenase metabolism of arachidonic acid. The role of the eicosanoids in mediating inflammation and gastrointestinal integrity is delineated. Evidence is presented regarding action of licofelone, one COX/LOX inhibitor that is currently in advanced stages of clin. trials. This review examines the hypothesis that licofelone is an effective anti-inflammatory agent that does not cause peptic damage.

CC 1-0 (Pharmacology)

ST review **cyclooxygenase** lipoxygenase **dual** **inhibitor** antiinflammatory

IT **Anti-inflammatory agents**
Drug targets
Human
(**cyclooxygenase**-lipoxygenase **dual** **inhibition** as emerging new therapy for inflammation)

IT 156897-06-2, Licofelone
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**cyclooxygenase**-lipoxygenase **dual** **inhibition** as emerging new therapy for inflammation)

IT **39391-18-9**, Cyclo-oxygenase **80619-02-9**, 5-**Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**cyclooxygenase**-lipoxygenase **dual** **inhibition** as emerging new therapy for inflammation)

IT **39391-18-9**, Cyclo-oxygenase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**cyclooxygenase**-lipoxygenase **dual** **inhibition** as emerging new therapy for inflammation)

RN 39391-18-9 HCAPLUS

CN Synthetase, prostaglandin endoperoxide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **39391-18-9**, Cyclo-oxygenase **80619-02-9**, 5-**Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**cyclooxygenase**-lipoxygenase **dual** **inhibition** as emerging new therapy for inflammation)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L201 ANSWER 5 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:476991 HCAPLUS

DOCUMENT NUMBER: 139:373904

TITLE: Therapeutic role of **dual** inhibitors of 5-LOX and COX, selective and non-selective non-steroidal anti-inflammatory drugs

AUTHOR(S): Martel-Pelletier, J.; Lajeunesse, D.; Reboul, P.; Pelletier, J.-P.

CORPORATE SOURCE: Osteoarthritis Research Unit, Hopital Notre-Dame, Centre hospitalier de l'Universite de Montreal, Montreal, QC, H2L 4M1, Can.

SOURCE: Annals of the Rheumatic Diseases (2003), 62(6), 501-509
CODEN: ARDIAO; ISSN: 0003-4967

PUBLISHER: BMJ Publishing Group

DOCUMENT TYPE: Journal; **General Review**

LANGUAGE: English

AB A review. **Dual** 5-LOX/COX inhibitors are potential new drugs to treat inflammation. They act by blocking the formation of both prostaglandins and leucotrienes but do not affect lipoxin formation. Such **combined** inhibition avoids some of the disadvantages of selective COX-2 inhibitors and spares the gastrointestinal mucosa.
CC 1-0 (Pharmacology)
ST review **cyclooxygenase** lipoxygenase **inhibitor** NSAIDs antiinflammatory
IT Leukotrienes
Prostaglandins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(blocking of prostaglandins; therapeutic role of **dual** inhibitors of 5-LOX and COX, selective and non-selective non-steroidal anti-inflammatory drugs)
IT Digestive tract
(mucosa, spare; therapeutic role of **dual** inhibitors of 5-LOX and COX, selective and non-selective non-steroidal anti-inflammatory drugs)
IT **Anti-inflammatory agents**
(nonsteroidal; therapeutic role of **dual** inhibitors of 5-LOX and COX, selective and non-selective non-steroidal anti-inflammatory drugs)
IT **Anti-inflammatory agents**
Human
(therapeutic role of **dual** inhibitors of 5-LOX and COX, selective and non-selective non-steroidal anti-inflammatory drugs)
IT **39391-18-9, Cyclooxygenase 80619-02-9, 5-Lipoxygenase** 329900-75-6, COX-2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; therapeutic role of **dual inhibitors** of 5-LOX and COX, selective and non-selective non-steroidal anti-inflammatory drugs)
IT **39391-18-9, Cyclooxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; therapeutic role of **dual inhibitors** of 5-LOX and COX, selective and non-selective non-steroidal anti-inflammatory drugs)
RN 39391-18-9 HCAPLUS
CN Synthetase, prostaglandin endoperoxide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **39391-18-9, Cyclooxygenase 80619-02-9, 5-Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; therapeutic role of **dual inhibitors** of 5-LOX and COX, selective and non-selective non-steroidal anti-inflammatory drugs)
REFERENCE COUNT: 103 THERE ARE 103 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L201 ANSWER 6 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:415269 HCAPLUS
DOCUMENT NUMBER: 139:345131
TITLE: Prevention of thrombosis and vascular inflammation: benefits and limitations of selective or **combined** COX-1, COX-2 and 5-LOX inhibitors
AUTHOR(S): de Gaetano, Giovanni; Donati, Maria Benedetta; Cerletti, Chiara
CORPORATE SOURCE: Center for High Technology Research and Education in

Biomedical Sciences, Catholic University, Campobasso, 86100, Italy
SOURCE: Trends in Pharmacological Sciences (2003), 24(5), 245-252
CODEN: TPHSDY; ISSN: 0165-6147
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Anti-thrombotic therapy with aspirin, which at low doses acts as a selective **inhibitor** of platelet **cyclooxygenase** 1 (COX-1) activity, is well established. However, a major limitation of aspirin treatment is its gastrointestinal toxicity, which is thought to be linked to the suppression of COX-1-mediated production of cytoprotective prostaglandins. Selective COX-2 inhibitors are effective anti-inflammatory agents with lower gastrointestinal toxicity than aspirin. These inhibitors might also downregulate vascular and leukocyte inflammatory components that play a major part in atherothrombotic disease. However, some selective COX-2 inhibitors appear to increase cardiovascular risk. Newly developed **dual** COX-**5-lipoxygenase** (5-LOX) **inhibitors** share the anti-inflammatory effect and gastric safety of COX-2 inhibitors, but also inhibit COX-1-mediated platelet function and 5-LOX-mediated synthesis of gastrotoxic leukotrienes. **Dual** inhibitors might thus be beneficial in the treatment of atherosclerosis, where platelet-leukocyte interaction dominates the underlying inflammatory process.

CC 1-0 (Pharmacology)
ST review **cyclooxygenase** lipoxygenase **inhibitor** antiinflammatory anticoagulant thrombosis atherosclerosis

IT Platelet (blood)
(activation; selective or **combined** COX-1, COX-2 and 5-LOX inhibitors in prevention of thrombosis and vascular inflammation)

IT Digestive tract, disease
(gastrointestinal toxicity; selective or **combined** COX-1, COX-2 and 5-LOX inhibitors in prevention of thrombosis and vascular inflammation)

IT Leukotrienes
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; selective or **combined** COX-1, COX-2 and 5-LOX inhibitors in prevention of thrombosis and vascular inflammation)

IT **Anti-inflammatory agents**
(nonsteroidal; selective or **combined** COX-1, COX-2 and 5-LOX inhibitors in prevention of thrombosis and vascular inflammation)

IT Cell activation
(platelet; selective or **combined** COX-1, COX-2 and 5-LOX inhibitors in prevention of thrombosis and vascular inflammation)

IT Cardiovascular system, disease
(risk of; selective or **combined** COX-1, COX-2 and 5-LOX inhibitors in prevention of thrombosis and vascular inflammation)

IT Anticoagulants
Atherosclerosis
Human
Thrombosis
(selective or **combined** COX-1, COX-2 and 5-LOX inhibitors in prevention of thrombosis and vascular inflammation)

IT **80619-02-9**, **5-Lipoxygenase** 329900-75-6, **Cyclooxygenase** 2 329967-85-3, **Cyclooxygenase** 1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; selective or **combined** COX-1, COX-2 and 5-LOX inhibitors in prevention of thrombosis and vascular inflammation)

IT 50-78-2, Aspirin

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(selective or **combined** COX-1, COX-2 and 5-LOX inhibitors in prevention of thrombosis and vascular inflammation)

IT **80619-02-9, 5-Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; selective or **combined** COX-1, COX-2 and 5-LOX inhibitors in prevention of thrombosis and vascular inflammation)

RN 80619-02-9 HCAPLUS
CN Oxygenase, arachidonate 5-lip- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **80619-02-9, 5-Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; selective or **combined** COX-1, COX-2 and 5-LOX inhibitors in prevention of thrombosis and vascular inflammation)

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L201 ANSWER 7 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:627078 HCAPLUS
DOCUMENT NUMBER: 138:180026
TITLE: Strategies to safely interfere with prostanoid activity while avoiding adverse renal effects: could COX-2 and COX-LOX **dual** inhibition be the answer?
AUTHOR(S): Gambaro, Giovanni
CORPORATE SOURCE: Department of Medical and Surgical Sciences, Division of Nephrology, University Hospital, Padua, Italy
SOURCE: Nephrology, Dialysis, Transplantation (2002), 17(7), 1159-1162
CODEN: NDTREA; ISSN: 0931-0509
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. The authors discuss the role of cyclooxygenase-2 (COX-2) in renal pathol., the role of leukotrienes in renal disease, putative risks of selective inhibition of prostanoid synthetic pathways, and COX-lipoxygenase (LOX) **dual** inhibition.

CC 1-0 (Pharmacology)

ST review nonsteroidal antiinflammatory **cyclooxygenase** 2 lipoxygenase **inhibitor**

IT **Anti-inflammatory agents**
(nonsteroidal; strategies to safely interfere with prostanoid activity while avoiding adverse renal effects in relation to **cyclooxygenase**-2 and **cyclooxygenase**-lipoxygenase **inhibition**)

IT Prostaglandins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prostanoids; strategies to safely interfere with prostanoid activity while avoiding adverse renal effects in relation to **cyclooxygenase**-2 and **cyclooxygenase**-lipoxygenase **inhibition**)

IT Kidney, disease
(strategies to safely interfere with prostanoid activity while avoiding adverse renal effects in relation to **cyclooxygenase**-2 and **cyclooxygenase**-lipoxygenase **inhibition**)

IT **80619-02-9, 5-Lipoxygenase** 329900-75-6, **Cyclooxygenase**-2
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(**inhibitors**; strategies to safely interfere with prostanoid activity while avoiding adverse renal effects in relation to **cyclooxygenase**-2 and **cyclooxygenase**-lipoxygenase **inhibition**)

IT **80619-02-9, 5-Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; strategies to safely interfere with prostanoid activity while avoiding adverse renal effects in relation to **cyclooxygenase**-2 and **cyclooxygenase**-lipoxygenase **inhibition**)

RN 80619-02-9 HCAPLUS
CN Oxygenase, arachidonate 5-lip- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **80619-02-9, 5-Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; strategies to safely interfere with prostanoid activity while avoiding adverse renal effects in relation to **cyclooxygenase**-2 and **cyclooxygenase**-lipoxygenase **inhibition**)

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L201 ANSWER 8 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:435244 HCAPLUS
DOCUMENT NUMBER: 137:319850
TITLE: Selective COX-2 inhibitors and **dual** acting anti-inflammatory drugs: Critical remarks
AUTHOR(S): Bertolini, A.; Ottani, A.; Sandrini, M.
CORPORATE SOURCE: Section of Clinical Pharmacology and Toxicology, Department of Medicine, University of Modena and Reggio Emilia, Modena, 41100, Italy
SOURCE: Current Medicinal Chemistry (2002), 9(10), 1033-1043
CODEN: CMCHE7; ISSN: 0929-8673
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Non steroidal anti-inflammatory drugs (NSAIDs) are still the most commonly used remedies for rheumatic diseases. But NSAIDs produce serious adverse effects, the most important being gastric injury up to gastric ulceration and renal damage. Several strategies were adopted to avoid these shortcomings, expecially gastrointestinal toxicity. So, non steroidal anti-inflammatory drugs were associated with gastroprotective agents that counteract the damaging effects of prostaglandin synthesis suppression: however, a **combination** therapy introduces problems of pharmacokinetics, toxicity, and patient's compliance. Also incorporation of a NO-generating moiety into the mol. of several NSAIDs was shown to greatly attenuate their ulcerogenic activity: however, several findings suggest a possible involvement of NO in the pathogenesis of arthritis and subsequent tissue destruction. A most promising approach seemed to be the preparation of novel NSAIDs, specific for the inducible isoform of cyclooxygenase (COX-2): they appear to be devoid of gastrointestinal toxicity, in that they spare mucosal prostaglandin synthesis. However, a number of recent studies raised serious questions about the 2 central tenets that support this approach, namely that the prostaglandins that mediate inflammation and pain are produced solely via COX-2 and that the prostaglandins that are important in gastrointestinal and renal function are produced solely via COX-1. So, increasing evidence shows that COX-2 (not only COX-1) also plays a physiol. role in several body functions and that, conversely, COX-1 (not only COX-2) may also be

induced at sites of inflammation. Moreover, COX-2 selective NSAIDs have lost the cardiovascular protective effects of non-selective NSAIDs, effects which are mediated through COX-1 inhibition (in addition, COX-2 has a role in sustaining vascular prostacyclin production). The products generated by the 5-lipoxygenase pathway (leukotrienes) are particularly important in inflammation: indeed, leukotrienes increase microvascular permeability and are potent chemotactic agents; moreover, **inhibition** of **5-lipoxygenase** indirectly reduces the expression of TNF-α (a cytokine that plays a key role in inflammation). This explains the efforts to obtain drugs able to **inhibit** both **5-lipoxygenase** and **cyclooxygenases**: the so-called **dual** acting anti-inflammatory drugs. Such compds. retain the activity of classical NSAIDs, while avoiding their main drawbacks, in that curtailed production of gastroprotective prostaglandins is associated with a concurrent curtailed production of the gastro-damaging and bronchoconstrictive leukotrienes. Moreover, thanks to their mechanism of action, **dual** acting anti-inflammatory drugs could not merely alleviate symptoms of rheumatic diseases, but might also satisfy, at least in part, the criteria of curative drugs. Indeed, leukotrienes are pro-inflammatory, increase microvascular permeability, are potent chemotactic agents and attract eosinophils, neutrophils and monocytes into the synovium. Finally, recent data strongly suggest that **dual** inhibitors may have specific protective activity also in neurodegeneration.

CC 1-0 (Pharmacology)

ST review **cyclooxygenase** lipooxygenase **inhibitor** NSAID antirheumatic

IT **Anti-inflammatory agents**
(nonsteroidal; selective COX-2 inhibitors and **dual** acting anti-inflammatory drugs)

IT **Antirheumatic agents**
(selective COX-2 inhibitors and **dual** acting anti-inflammatory drugs)

IT **80619-02-9**, **5-Lipoxygenase** 329900-75-6, **Cyclooxygenase** 2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitor**; selective COX-2 **inhibitors** and **dual** acting anti-inflammatory drugs)

IT **80619-02-9**, **5-Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitor**; selective COX-2 **inhibitors** and **dual** acting anti-inflammatory drugs)

RN 80619-02-9 HCAPLUS

CN Oxygenase, arachidonate 5-lip- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **80619-02-9**, **5-Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitor**; selective COX-2 **inhibitors** and **dual** acting anti-inflammatory drugs)

REFERENCE COUNT: 127 THERE ARE 127 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L201 ANSWER 9 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:136698 HCAPLUS

DOCUMENT NUMBER: 136:395185

TITLE: Non steroidal anti-inflammatory and anti-allergy agents

AUTHOR(S): Kontogiorgis, C. A.; Hadjipavlou-Litina, D. J.

CORPORATE SOURCE: Department of Pharmaceutical Chemistry, School of

Pharmacy, Aristotelian University of Thessaloniki, Thessaloniki, 54006, Greece
SOURCE: Current Medicinal Chemistry (2002), 9(1), 89-98
CODEN: CMCHE7; ISSN: 0929-8673
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Non steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used for inflammation therapy. The major drawback in using the NSAIDs is in their tendency to cause gastrointestinal toxicity. Since the roles of arachidonic acid (A.A) metabolites, as leukotrienes (Lts), prostaglandins (PGs) and thromboxanes (TXA2) as mediators of the inflammatory reaction were clarified, much effort has been made to develop inhibitors of the production of these chemical mediators as anti-inflammatory agents. These mediators also play important roles in some inflammatory or allergic diseases, acting either alone or in **combination** and **inhibitors** of **5-lipoxygenase** (5-LOX) and/or cyclooxygenase isoforms 1,2 (COX-1,2) may be useful for the treatment of asthma, psoriasis and rheumatoid arthritis. Leukotrienes, the products of 5-LOX metabolism have been associated with immediate hypersensitivity reactions, anaphylaxis and asthma. In addition, active oxygen species (AOS) including superoxide anion (O2-), hydrogen peroxide, hydroxyl radical and ferric radical, mediate cell damage in a variety of pathophysiol. conditions and are responsible for oxidative injury of enzymes, lipid membranes and DNA in living cells and tissues. Prostaglandins and leukotrienes in the arachidonate pathway linked with lipid peroxidn. may amplify the oxidative damage. Nitric oxide (NO) plays also a role as an effector in inflammation, since PG and NO thought to be important in maintaining mucosal integrity. **Dual** or selective inhibitors, specific receptor antagonists, AOS scavengers, and NO donors have been under development for therapeutic application. Several classes of inhibitors have been identified and at least 12 major chemical series are known to affect PGs production directly. In this review, we account on our research work concerning NSAIDs **combined** with a reference of the recent literature.
CC 1-0 (Pharmacology)
ST review nonsteroidal antiinflammatory **cyclooxygenase inhibitor** allergy
IT **Anti-inflammatory agents**
(nonsteroidal; non steroidal anti-inflammatory and anti-allergy agents)
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L201 ANSWER 10 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:921233 HCAPLUS
DOCUMENT NUMBER: 137:72356
TITLE: Pros and cons of selective **inhibition** of **cyclooxygenase**-2 versus **dual** lipoxygenase/**cyclooxygenase** **inhibition**: Is two better than one?
AUTHOR(S): Parente, Luca
CORPORATE SOURCE: Dep. of Pharmacology Sci., Univ. of Salerno, Fisciano(Salerno), 84084, Italy
SOURCE: Journal of Rheumatology (2001), 28(11), 2375-2382
CODEN: JRHUA9; ISSN: 0315-162X
PUBLISHER: Journal of Rheumatology Publishing Co. Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review on the two targets of drug action, cyclooxygenase-2 and

5-lipoxygenase (5-LOX), evaluating both the effects and the clin. implications of the inhibition of the single enzymes vs. the **combined dual** inhibition of the two enzymes. Incidence of unwanted gastrointestinal (GI) effects are reduced with the highly selective COX-2 inhibitors compared to classical nonspecific COX inhibitors. The prostaglandins produced by COX-2 are involved in various physiol. housekeeping functions like adaptive cytoprotection in the GI mucosa, synthesis of antiaggregatory PGI2 by endothelial cells, formation of vasodilatory PGE2 in the kidney, and regulation of the reproductive processes. In exptl. settings, **dual** 5-LOX/COX inhibitors are potent antiinflammatory drugs. The pharmacol. profile of **dual** 5-LOX/COX inhibitors is similar to that of antiinflammatory glucocorticoids, which inhibit phospholipase A2 (PLA2), and prevent arachidonic acid metabolism by both COX and 5-LOX. **Dual** inhibitors do not affect intermediate metabolism or endocrine functions, do not lead to severe side effects normally related with the use of glucocorticoids, and show protective effects on GI mucosa.

CC 1-0 (Pharmacology)

ST review **cyclooxygenase** lipooxygenase **dual** **inhibitor** gastrointestinal tract

IT Digestive tract
(mucosa; pros and cons of selective **inhibition** of **cyclooxygenase**-2 vs. **dual** lipoxygenase/COX **inhibition**)

IT **Anti-inflammatory agents**
(nonsteroidal; pros and cons of selective **inhibition** of **cyclooxygenase**-2 vs. **dual** lipoxygenase/COX **inhibition**)

IT **80619-02-9**, **5-Lipoxygenase** 329900-75-6, **Cyclooxygenase**-2
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**inhibitors**; pros and cons of selective **inhibition** of **cyclooxygenase**-2 vs. **dual** lipoxygenase/COX **inhibition**)

IT **80619-02-9**, **5-Lipoxygenase**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**inhibitors**; pros and cons of selective **inhibition** of **cyclooxygenase**-2 vs. **dual** lipoxygenase/COX **inhibition**)

RN 80619-02-9 HCAPLUS

CN Oxygenase, arachidonate 5-lip- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **80619-02-9**, **5-Lipoxygenase**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**inhibitors**; pros and cons of selective **inhibition** of **cyclooxygenase**-2 vs. **dual** lipoxygenase/COX **inhibition**)

REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L201 ANSWER 11 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:890258 HCAPLUS

DOCUMENT NUMBER: 137:118810

TITLE: **Dual** acting anti-inflammatory drugs: a reappraisal

AUTHOR(S): Bertolini, A.; Ottani, A.; Sandrini, M.

CORPORATE SOURCE: Department of Biomedical Sciences, Section of Pharmacology, University of Modena and Reggio Emilia, Modena, 41100, Italy
SOURCE: Pharmacological Research (2001), 44(6), 437-450
CODEN: PHMREP; ISSN: 1043-6618
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Rheumatic diseases are the most prevalent causes of disability in western countries, and non-steroidal anti-inflammatory drugs (NSAIDs) are still the most commonly used remedies. However, NSAIDs cause several serious adverse effects, the most important being from gastric injury to gastric ulceration and renal damage. Attempts to develop non-steroidal anti-inflammatory remedies devoid of these shortcomings-especially gastrointestinal toxicity-have followed several strategies. Non-steroidal anti-inflammatory drugs have, therefore, been associated with gastroprotective agents that counteract the damaging effects of prostaglandin synthesis suppression; however, a **combination** therapy introduces other problems of pharmacokinetics, toxicity, and patient's compliance. More recently, incorporation of a nitric oxide (NO)-generating moiety into the mol. of several NSAIDs was shown to greatly attenuate their ulcerogenic activity; however, several findings suggest a possible involvement of NO in the pathogenesis of arthritis and subsequent tissue destruction. A most promising approach seemed to be the preparation of novel NSAIDs, targeted at the inducible isoform of prostaglandin synthase (COX-2); they appear to be devoid of gastrointestinal toxicity, in that they spare mucosal prostaglandin synthesis. However, a number of recent studies have raised serious questions about the two central tenets that support this approach, namely that the prostaglandins that mediate inflammation and pain are produced solely via COX-2 and that the prostaglandins that are important in gastrointestinal and renal function are produced solely via COX-1. So, a growing body of evidence shows that COX-2 (not only COX-1) also plays a physiol. role in several body functions and that, conversely, COX-1 (not only COX-2) may also be induced at sites of inflammation. More recent and puzzling data shows that COX-2 is induced during the resolution of an inflammatory response, and at this point it produces anti-inflammatory (PGD 2and PGF 2α), but not proinflammatory (PGE 2) prostaglandins; inhibition of COX-2 at this point thus results in persistence of the inflammation. Moreover, COX-2 selective NSAIDs have lost the cardiovascular protective effects of non-selective NSAIDs, effects which are mediated through COX-1 inhibition (in addition, COX-2 has a role in sustaining vascular prostacyclin production). The generation of other very important products of the arachidonic acid cascade (besides **cyclooxygenase**-produced metabolites) is **inhibited** neither by non-selective nor by COX-2 selective NSAIDs. The products generated by the 5-lipoxygenase pathway (leukotrienes) are particularly important in inflammation; indeed, leukotrienes increase microvascular permeability and are potent chemotactic agents. Moreover, **inhibition** of **5-lipoxygenase** indirectly reduces the expression of TNF- α(a cytokine that plays a key role in inflammation). These data and considerations explain the efforts to obtain drugs able to **inhibit** both **5-lipoxygenase** and **cyclooxygenases**, the so-called **dual** acting anti-inflammatory drugs. Such compds. retain the activity of classical NSAIDs, while avoiding their main drawbacks, in that curtailed production of gastroprotective prostaglandins is associated with a concurrent curtailed production of the gastro-damaging and bronchoconstrictive leukotrienes. Moreover, thanks to their mechanism of action, **dual** acting anti-inflammatory drugs could not merely alleviate symptoms of rheumatic diseases, but might also satisfy, at least in part, the criteria

of a more definitive treatment. Indeed, leukotrienes are pro-inflammatory, increase microvascular permeability, are potent chemotactic agents and attract eosinophils, neutrophils and monocytes into the synovium. (c) 2001 The Italian Pharmacological Society.

CC 1-0 (Pharmacology)

ST review **dual** acting antiinflammatory antirheumatic cycloxygenase lipoxygenase

IT **Antirheumatic agents**
Osteoarthritis
Rheumatic diseases
(**dual** acting anti-inflammatory drugs)

IT Prostaglandins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**dual** acting anti-inflammatory drugs)

IT **Anti-inflammatory agents**
(nonsteroidal; **dual** acting anti-inflammatory drugs)

IT 10102-43-9, Nitrogen oxide (NO), biological studies 80619-02-9, 5-Lipoxygenase 329900-75-6, COX 2 329967-85-3, COX-1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**dual** acting anti-inflammatory drugs)

REFERENCE COUNT: 127 THERE ARE 127 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L201 ANSWER 12 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:866463 HCAPLUS
DOCUMENT NUMBER: 136:193458
TITLE: **Dual inhibitors** of **cyclooxygenase** and **5-lipoxygenase.** A new avenue in anti-inflammatory therapy?
AUTHOR(S): Fiorucci, Stefano; Meli, Rosaria; Bucci, Mariarosaria; Cirino, Giuseppe
CORPORATE SOURCE: Sezione di Gastroenterologia ed Epatologia, Dipartimento di Medicina Clinica e Sperimentale, Universita delgi Studi di Perugia, Perugia, Italy
SOURCE: Biochemical Pharmacology (2001), 62(11), 1433-1438
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review is given. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a mainstay in the treatment of inflammatory disease and are among the most widely used drugs worldwide. They are anti-inflammatory, antipyretic, and analgesic and are prescribed as 1st choice for the treatment of rheumatic disorders and, in general, inflammation. The main limitation in using NSAIDs consists in their side-effects, including gastrointestinal ulcerogenic activity and bronchospasm. The mechanism of action of these drugs is attributed to the **inhibition** of **cyclooxygenase** (COX), and, consequently, the conversion of arachidonic acid into prostaglandins. It is hypothesized that the undesirable side-effects of NSAIDs are due to the inhibition of COX-1 (constitutive isoform), whereas the beneficial effects are related to the inhibition of COX-2 (inducible isoform). Arachidonic acid can also be converted to leukotrienes (LTs) by the action of 5-lipoxygenase (5-LOX). LTC4, LTD4, and LTE4 are potent bronchoconstrictors, whereas LTB4 is chemotactic for leukocytes and plays an important role in the development of gastrointestinal ulcers by contributing to the inflammatory process. Thus, developing **dual** inhibitor compds. that will simultaneously inhibit COX and 5-LOX could enhance their individual anti-inflammatory effects and reduce the

undesirable side-effects associated with NSAIDs, especially of the gastrointestinal tract. The most promising COX/5-LOX inhibitor is ML3000 ([2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl]-acetic acid), now in Phase III clin. trials. This new approach will certainly help to unravel the mechanisms at the root of the undesirable effects of NSAIDs and to develop safer NSAIDs.

CC 1-0 (Pharmacology)

ST review **cyclooxygenase** lipoxygenase **inhibitor** NSAID

IT **Anti-inflammatory agents**
(nonsteroidal; **dual inhibitors** of **cyclooxygenase** and **5-lipoxygenase**)

IT **39391-18-9**, **Cyclooxygenase** **80619-02-9**, **5-Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**dual inhibitors** of **cyclooxygenase** and **5-lipoxygenase**)

IT **39391-18-9**, **Cyclooxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**dual inhibitors** of **cyclooxygenase** and **5-lipoxygenase**)

RN 39391-18-9 HCAPLUS

CN Synthetase, prostaglandin endoperoxide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **39391-18-9**, **Cyclooxygenase** **80619-02-9**, **5-Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**dual inhibitors** of **cyclooxygenase** and **5-lipoxygenase**)

REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L201 ANSWER 13 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:554481 HCAPLUS

DOCUMENT NUMBER: 135:326833

TITLE: Discovery and development of ML3000

AUTHOR(S): Laufer, Stefan

CORPORATE SOURCE: Institute of Pharmacy, University of Tuebingen, Tuebingen, D-72076, Germany

SOURCE: Inflammopharmacology (2001), 9(1-2), 101-112
CODEN: IAOAES; ISSN: 0925-4692

PUBLISHER: VSP BV

DOCUMENT TYPE: Journal; **General Review**

LANGUAGE: English

AB A review, with refs. NSAID management of the inflammatory process has focused on reducing the production of inflammatory prostaglandins by **inhibiting** the **cyclooxygenase** (COX) enzyme. However, blocking COX also reduces gastroprotective prostaglandins, causing the well-known gastrointestinal side effects. Furthermore, a shunting of arachidonic acid to the 5-lipoxygenase (5-LOX) pathway may also occur, causing an increase in leukotrienes and further GI damage. Several compds., designed to block both COX and 5-LOX, have failed in clin. trials due to liver toxicity, related to their redox potential. ML3000 is a new pyrrolizine compound resulting from a systematic approach to design a non-redox substrate analog of arachidonic acid that inhibited both COX and 5-LOX. Pharmacodynamic studies determined that ML3000 is a **dual** inhibitor of COX and 5-LOX, with analgesic, anti-inflammatory, antipyretic, antiplatelet, and anti-bronchoconstrictive activity, and minimal gastrointestinal side effects. Clin. studies show efficacy in

osteoarthritis and excellent gastrointestinal safety. ML3000 is now in phase III development.
CC 1-0 (Pharmacology)
ST review ML3000 **cyclooxygenase** lipoxygenase **inhibitor** antiinflammatory
IT Analgesics
Antiarthritics
Antiasthmatics
Antipyretics
Platelet aggregation **inhibitors**
(**cyclooxygenase** and lipoxygenase **inhibitor** ML3000 discovery, efficacy and safety in humans)
IT Digestive tract
(disease; **cyclooxygenase** and lipoxygenase **inhibitor** ML3000 discovery, efficacy and safety in humans)
IT **Anti-inflammatory agents**
(nonsteroidal; **cyclooxygenase** and lipoxygenase **inhibitor** ML3000 discovery, efficacy and safety in humans)
IT 156897-06-2, ML3000
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**cyclooxygenase** and lipoxygenase **inhibitor** ML3000 discovery, efficacy and safety in humans)
IT **39391-18-9, Cyclooxygenase 80619-02-9, 5-Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors; cyclooxygenase** and lipoxygenase **inhibitor** ML3000 discovery, efficacy and safety in humans)
IT **39391-18-9, Cyclooxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors; cyclooxygenase** and lipoxygenase **inhibitor** ML3000 discovery, efficacy and safety in humans)
RN 39391-18-9 HCAPLUS
CN Synthetase, prostaglandin endoperoxide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **39391-18-9, Cyclooxygenase 80619-02-9, 5-Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors; cyclooxygenase** and lipoxygenase **inhibitor** ML3000 discovery, efficacy and safety in humans)
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L201 ANSWER 14 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:411272 HCAPLUS
DOCUMENT NUMBER: 136:240847
TITLE: Anti-inflammatory drugs: new multitarget compounds to face an old problem. The **dual** inhibition concept
AUTHOR(S): Celotti, Fabio; Laufer, Stefan
CORPORATE SOURCE: Institute of Endocrinology, University of Milano, Italy
SOURCE: Pharmacological Research (2001), 43(5), 429-436
CODEN: PHMREP; ISSN: 1043-6618
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. In this short review we have tried to focus on some new

relevant aspects of the pharmacol. control of inflammation. The clin. availability of new drugs able to produce a selective **inhibition** of type 2 **cyclooxygenase** (COX-2), the enzyme thought to be mainly responsible for generating arachidonic-acid-derived inflammatory mediators, has been the origin of much hope. However, expectations of having an effective and completely safe non-steroidal anti-inflammatory drug (NSAID) have been only partially fulfilled. Emerging information has challenged some aspects of the original hypothesis indicating COX-2 as devoid of 'housekeeping' physiol. functions. Moreover, the recently available clin. studies have indicated only a relatively small improvement in the tolerability of the newer 'selective' COX-2 inhibitors over the classical COX-1/COX-2 **mixed** type NSAIDs. The new appreciation of the role of other arachidonic acid derivs., the leukotrienes (LTS), in producing and maintaining inflammation has generated considerable interest in drugs able to block LTS receptors or to produce a selective **inhibition** of **5-lipoxygenase** (5-LO), the initial key enzyme of the leukotriene pathway. These drugs are now included among the effective therapies of asthma but appear, in the few clin. studies performed, to be an insufficient single therapeutic approach in other inflammatory diseases. Drugs able to block equally well both COX and 5-LO metabolic pathways (**dual** inhibitors) have been developed and exptl. evaluated in the last few years, but none are available on the market yet. The pharmacol. rationale at the basis of their development is strong, and animal studies are indicative of a wide range of anti-inflammatory activity. What appears most impressive from the available studies on **dual** inhibitors is their almost complete lack of gastric toxicity, the most troublesome side effect of NSAIDs. The mechanism of the gastric-sparing properties of these drugs is not yet completely understood; however, it appears that leukotrienes significantly contribute to gastric epithelial injury particularly when these compds. represent the major arachidonic acid derivs. present in the gastric mucosa after inhibition of prostanoid production (c) 2001 The Italian Pharmacological Society.

CC 1-0 (Pharmacology)

IT **Anti-inflammatory agents**
(nonsteroidal; antiinflammatory drugs and **dual** inhibition concept)

IT 80619-02-9, **5-Lipoxygenase** 329900-75-6, Cox 2
329967-85-3, COX 1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antiinflammatory drugs and **dual inhibition** concept)

REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L201 ANSWER 15 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:429621 HCAPLUS
DOCUMENT NUMBER: 133:129369
TITLE: Cellular actions of opioids and other analgesics: implications for **synergism** in pain relief
AUTHOR(S): Christie, MacDonald J.; Connor, Mark; Vaughan, Christopher W.; Ingram, Susan L.; Bagley, Elena E.
CORPORATE SOURCE: The Medical Foundation, The University of Sydney, Sydney, 2006, Australia
SOURCE: Clinical and Experimental Pharmacology and Physiology (2000), 27(7), 520-523
CODEN: CEXPB9; ISSN: 0305-1870
PUBLISHER: Blackwell Science Asia Pty Ltd.
DOCUMENT TYPE: Journal; **General Review**

LANGUAGE: English

AB A review with 31 refs. 1. μ-Opioid receptor agonists mediate their central analgesic effects by actions on neurons within brain regions such as the mid-brain periaqueductal gray (PAG). Within the PAG, μ-opioid receptor-mediated analgesia results from inhibition of GABAergic influences on output projection neurons. The authors have established that μ-opioid receptor activation in the PAG causes a presynaptic inhibition of GABA release that is mediated by activation of a voltage-dependent K+ channel via 12-lipoxygenase (LOX) metabolites of arachidonic acid. 2. At a cellular level, μ-opioid agonists have also been shown to open inwardly rectifying K+ channels, close voltage-gated Ca2+ channels and presynaptically inhibit glutamatergic synaptic transmission in the PAG. 3. The μ-opioid receptor-mediated presynaptic inhibition of GABAergic transmission was abolished by phospholipase A2 inhibitors and non-specific LOX and specific 12-LOX inhibitors. Cyclo-oxygenase (COX) and specific 5-LOX inhibitors did not reduce the inhibitory effects of μ-opioid agonists. 4. The opioid actions on GABAergic transmission were mimicked by arachidonic acid and 12-LOX metabolites, but not 5-LOX metabolites. The efficacy of μ-opioids was enhanced **synergistically** by treatment of PAG neurons with inhibitors of the other major enzymes responsible for arachidonic acid metabolism, COX and 5-LOX. 5. These results explain a previously described analgesic action of COX inhibitors in the central nervous system that was both independent of prostanoid release and inhibited by opioid receptor antagonists and they also explain the **synergistic** interaction of opioids with COX inhibitors. These findings also suggest new avenues for the development of centrally active analgesic agents involving **combinations** of lowered doses of opioids and specific 5-LOX inhibitors.

CC 1-0 (Pharmacology)

ST review opioid analgesic cellular action **synergism**

IT Neurotransmission
(GABAergic; cellular actions of opioids and other analgesics and implications for **synergism** in pain relief)

IT Analgesics
(cellular actions of opioids and other analgesics and implications for **synergism** in pain relief)

IT Opioids
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cellular actions of opioids and other analgesics and implications for **synergism** in pain relief)

IT **Anti-inflammatory agents**
(nonsteroidal; cellular actions of opioids and other analgesics and implications for **synergism** in pain relief)

IT Drug interactions
(**synergistic**; cellular actions of opioids and other analgesics and implications for **synergism** in pain relief)

IT **39391-18-9, Cyclooxygenase 80619-02-9, 5-Lipoxygenase**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**inhibitors**; cellular actions of opioids and other analgesics and implications for **synergism** in pain relief)

IT **39391-18-9, Cyclooxygenase**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**inhibitors**; cellular actions of opioids and other analgesics and implications for **synergism** in pain relief)

RN 39391-18-9 HCAPLUS
CN Synthetase, prostaglandin endoperoxide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **39391-18-9, Cyclooxygenase 80619-02-9, 5-Lipoxygenase**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**inhibitors**; cellular actions of opioids and other analgesics and implications for **synergism** in pain relief)
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L201 ANSWER 16 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:477374 HCAPLUS
DOCUMENT NUMBER: 131:138672
TITLE: ML-3000 Merckle GmbH
AUTHOR(S): Chin, Beth; Wallace, John
CORPORATE SOURCE: AltaPharm International, Cochrane, AB, T0L 0W0, Can.
SOURCE: Current Opinion in Anti-Inflammatory and Immunomodulatory Investigational Drugs (1999), 1(2), 118-122
CODEN: COAIFF; ISSN: 1464-8474
PUBLISHER: Current Drugs Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 25 refs. Merckle's ML-3000, is a **dual cyclooxygenase** and **5-lipoxygenase inhibitor.** The compound is in phase II clin. trials for the treatment of inflammatory disorders such as rheumatoid arthritis (RA) and associated pain. The drug reduces prostaglandin synthesis without causing mucosal injury, although the mechanism of action is unclear. ML-3000 is one of the category of drugs known as double-acting anti-inflammatory drugs.
CC 1-0 (Pharmacology)
IT **Anti-inflammatory agents**
Antirheumatic agents
(antiinflammatory and antirheumatic activity of ML3000 in humans and laboratory animals)
IT **39391-18-9, Cyclooxygenase 80619-02-9, 5-Lipoxygenase**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(**inhibitor**; antiinflammatory and antirheumatic activity of ML3000 in humans and laboratory animals in relation to)
IT **39391-18-9, Cyclooxygenase**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(**inhibitor**; antiinflammatory and antirheumatic activity of ML3000 in humans and laboratory animals in relation to)
RN 39391-18-9 HCAPLUS
CN Synthetase, prostaglandin endoperoxide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **39391-18-9, Cyclooxygenase 80619-02-9, 5-Lipoxygenase**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(**inhibitor**; antiinflammatory and antirheumatic activity of ML3000 in humans and laboratory animals in relation to)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L201 ANSWER 17 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:711412 HCAPLUS
DOCUMENT NUMBER: 126:145
TITLE: **Dual inhibitors** of **5-lipoxygenase** and **cyclooxygenase**
AUTHOR(S): Connor, David T.; Boschelli, Diane H.
CORPORATE SOURCE: Department Chemistry, Parke-Davis, Pharmaceutical Research, Ann Arbor, MI, USA
SOURCE: Studies in Medicinal Chemistry (1996), 2(Biological Inhibitors), 47-86
CODEN: SMCHFE; ISSN: 1024-8056
PUBLISHER: Harwood
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review, with 185 refs., on **inhibitors** of **5-lipoxygenase** and **cyclooxygenase** which should down-regulate an inflammatory response. It appears that a **dual** inhibitor can be a superior anti-inflammatory drug.
CC 1-0 (Pharmacology)
ST review **cyclooxygenase** lipoxygenase **inhibitor** antiinflammatory
IT **Anti-inflammatory agents**
(**dual inhibitors** of lipoxygenase and **cyclooxygenase** as anti-inflammatory agents)
IT **39391-18-9**, **Cyclooxygenase 80619-02-9**, **5-Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors; dual inhibitors** of lipoxygenase and **cyclooxygenase** as anti-inflammatory agents)
IT **39391-18-9**, **Cyclooxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors; dual inhibitors** of lipoxygenase and **cyclooxygenase** as anti-inflammatory agents)
RN 39391-18-9 HCAPLUS
CN Synthetase, prostaglandin endoperoxide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **39391-18-9**, **Cyclooxygenase 80619-02-9**, **5-Lipoxygenase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors; dual inhibitors** of lipoxygenase and **cyclooxygenase** as anti-inflammatory agents)

L201 ANSWER 18 OF 18 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1987:526354 HCAPLUS
DOCUMENT NUMBER: 107:126354
TITLE: Inflammation and the mechanism of action of anti-inflammatory drugs
AUTHOR(S): Vane, John; Botting, Regina
CORPORATE SOURCE: Med. Coll., St. Bartholomew's Hosp., London, EC1M 6BQ, UK
SOURCE: FASEB Journal (1987), 1(2), 89-96
CODEN: FAJOEC; ISSN: 0892-6638
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 42 refs. including discussion on mediators of inflammation, the mechanism of actin of nonsteroidal and steroid anti-inflammatory

drugs, the role of **dual inhibition** of **cyclooxygenase** and **5-lipoxygenase**, and discussion specific agents.
CC 1-0 (Pharmacology)
Section cross-reference(s): 2, 4
IT **Inflammation inhibitors**
(mechanism of action of)
IT **Inflammation**
(pathophysiol. of, mediators in)

=> FIL STNGUIDE

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DICTIONARY FILE UPDATES: 28 JUL 2004 HIGHEST RN 718597-29-6

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=> fil zreg

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STRUCTURE FILE UPDATES: 28 JUL 2004 HIGHEST RN 718597-29-6
DICTIONARY FILE UPDATES: 28 JUL 2004 HIGHEST RN 718597-29-6

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/zregistryss.html

=> fil zcaplus

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FILE LAST UPDATED: 29 Jul 2004 (20040729/ED)

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=> fil hcaplus

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FILE COVERS 1907 - 30 Jul 2004 VOL 141 ISS 6
FILE LAST UPDATED: 29 Jul 2004 (20040729/ED)

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=> fil embase

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	[redacted]	[redacted]

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CA SUBSCRIBER PRICE	[redacted]	[redacted]

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FILE COVERS 1974 TO 29 Jul 2004 (20040729/ED)

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=> FIL STNGUIDE

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jul 23, 2004 (20040723/UP).

=> d que l163
L1             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  39391-18-9/RN
L2             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  80619-02-9/RN
L101(          1)SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2002-098644/AP,PRN
L102             SEL  PLU=ON  L101 1- RN :      169 TERMS
L103(        169)SEA FILE=REGISTRY ABB=ON  PLU=ON  L102
L104(          4)SEA FILE=REGISTRY ABB=ON  PLU=ON  L103 AND (C16H14N2O3S OR
                 C17H14O4S OR C16H9F5N2O3S OR C16H14N2O3S)/MF
L105(         13)SEA FILE=REGISTRY ABB=ON  PLU=ON  L103 AND (C17H14F3N3O3S OR
                 C17H12F4N2O4S OR C17H16N2O4S OR C16H11CLF3N3O2S OR C17H12F2O4S
                 OR C16H13F2NO4S OR C17H14F3N3O2S OR C16H12F3N3O2S OR C17H14F3N3
                 O2S OR C17H12BRFO2S2 OR C13H18N2O5S OR C16H13F3N4O2S OR
                 C14H13N3O4S2)/MF
L106(         17)SEA FILE=REGISTRY ABB=ON  PLU=ON  L104 OR L105
L107(         40)SEA FILE=REGISTRY ABB=ON  PLU=ON  (123653-11-2/CRN OR 162011-90
                 -7/CRN OR 169590-41-4/CRN OR 170569-86-5/CRN OR 177660-77-4/CRN
                  OR 177660-80-9/CRN OR 177660-92-3/CRN OR 181695-72-7/CRN OR
                 185344-51-8/CRN OR 185344-55-2/CRN OR 195061-34-8/CRN OR
                 195065-56-6/CRN OR 195065-57-7/CRN OR 71125-38-7/CRN OR
                 80937-31-1/CRN OR 88149-94-4/CRN OR 93014-16-5/CRN)
L108           57 SEA FILE=REGISTRY ABB=ON  PLU=ON  L106 OR L107
L109(           1)SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2002-098644/AP,PRN
L110             SEL  PLU=ON  L109 1- RN :      169 TERMS
L111          169 SEA FILE=REGISTRY ABB=ON  PLU=ON  L110
L112(           1)SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2002-098644/AP,PRN
L113             SEL  PLU=ON  L112 1- RN :      169 TERMS
L114(         169)SEA FILE=REGISTRY ABB=ON  PLU=ON  L113
L115(          32)SEA FILE=REGISTRY ABB=ON  PLU=ON  L114 AND MAN/CI
L116(          30)SEA FILE=REGISTRY ABB=ON  PLU=ON  L115 NOT (39391-18-9 OR
                 80619-02-9)/RN
L117(        1373)SEA FILE=REGISTRY ABB=ON  PLU=ON  CYCLOSPORIN/BI
L118         1403 SEA FILE=REGISTRY ABB=ON  PLU=ON  L116 OR L117
L120          122 SEA FILE=REGISTRY ABB=ON  PLU=ON  L111 NOT (L108 OR L118)
L121         4649 SEA FILE=EMBASE ABB=ON  PLU=ON  L108
L122              SEL  PLU=ON  L1 1- CHEM :       36 TERMS
L123        24834 SEA FILE=EMBASE ABB=ON  PLU=ON  L122
L124        12782 SEA FILE=EMBASE ABB=ON  PLU=ON  L123 (5A) (?INHIBIT? OR ?RUPT?
                 OR ?BLOCK? OR ?DISABL? OR ?STOP?)
L125        12513 SEA FILE=EMBASE ABB=ON  PLU=ON  L120
L126              SEL  PLU=ON  L2 1- CHEM :       10 TERMS
L127         3482 SEA FILE=EMBASE ABB=ON  PLU=ON  L126
L128         1801 SEA FILE=EMBASE ABB=ON  PLU=ON  L127 (5A) (?INHIBIT? OR ?RUPT?
                 OR ?BLOCK? OR ?DISABL? OR ?STOP?)
L129        62215 SEA FILE=EMBASE ABB=ON  PLU=ON  ?CYCLOSPORIN?
L130        59942 SEA FILE=EMBASE ABB=ON  PLU=ON  L118
L137         4200 SEA FILE=EMBASE ABB=ON  PLU=ON  ?ARACHIDON? (5A) (?INHIBIT? OR
                 ?RUPT? OR ?BLOCK? OR ?DISABL? OR ?STOP?)
L138        14598 SEA FILE=EMBASE ABB=ON  PLU=ON  L124 OR L121
L139        13039 SEA FILE=EMBASE ABB=ON  PLU=ON  L128 OR L125
L140        62410 SEA FILE=EMBASE ABB=ON  PLU=ON  L129 OR L130
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L141          37 SEA FILE=EMBASE ABB=ON  PLU=ON  L138 AND L139 AND L140
L142      284643 SEA FILE=EMBASE ABB=ON  PLU=ON  DRUG COMBINATION+PFT,NT/CT
L143          16 SEA FILE=EMBASE ABB=ON  PLU=ON  L141 AND L142
L146     1820982 SEA FILE=EMBASE ABB=ON  PLU=ON  (?INHIBIT? OR ?RUPT? OR
                 ?BLOCK? OR ?DISABL? OR ?STOP?)
L147       21871 SEA FILE=EMBASE ABB=ON  PLU=ON  PROSTAGLANDIN SYNTH?
L148        8380 SEA FILE=EMBASE ABB=ON  PLU=ON  L147 (5A) L146
L149       20129 SEA FILE=EMBASE ABB=ON  PLU=ON  CYCLOOXYGENAS?
L150       12425 SEA FILE=EMBASE ABB=ON  PLU=ON  L149 (5A) L146
L151       10946 SEA FILE=EMBASE ABB=ON  PLU=ON  ?LIPOXYGEN?
L152        5146 SEA FILE=EMBASE ABB=ON  PLU=ON  L151 (5A) L146
L153        6182 SEA FILE=EMBASE ABB=ON  PLU=ON  (COX2 OR COX-2)
L154        3833 SEA FILE=EMBASE ABB=ON  PLU=ON  L153 (5A) L146
L155       21155 SEA FILE=EMBASE ABB=ON  PLU=ON  L138 OR L148 OR L150 OR L154
L156       15381 SEA FILE=EMBASE ABB=ON  PLU=ON  L139 OR L152
L157        4997 SEA FILE=EMBASE ABB=ON  PLU=ON  L155 AND L156
L158        8569 SEA FILE=EMBASE ABB=ON  PLU=ON  L157 OR L137
L159          80 SEA FILE=EMBASE ABB=ON  PLU=ON  L158 AND L140
L160          35 SEA FILE=EMBASE ABB=ON  PLU=ON  L159/MAJ
L161     1819760 SEA FILE=EMBASE ABB=ON  PLU=ON  (MIX? OR ?MIXT? OR DUAL OR
                 ?COMBIN? OR ?COMPRIS? OR ?COMPOS? OR COMB OR COMPN OR DUAL OR
                 ?INTERACT? OR ?SYNERG? OR BLEND)
L162          12 SEA FILE=EMBASE ABB=ON  PLU=ON  L160 AND L161
L163          23 SEA FILE=EMBASE ABB=ON  PLU=ON  L162 OR L143

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L203          70 DUP REM L202 L163 (3 DUPLICATES REMOVED)
                 ANSWERS '1-50' FROM FILE HCAPLUS
                 ANSWERS '51-70' FROM FILE EMBASE

=> d ibib hitind abs 51

L203 ANSWER 51 OF 70  EMBASE  COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
     on STN
ACCESSION NUMBER:    2004191466  EMBASE
TITLE:               Urticaria and angioedema: An overview.
AUTHOR:              Dibbern Jr. D.A.; Dreskin S.C.
CORPORATE SOURCE:    Dr. S.C. Dreskin, Div. of Allerg. and Clin. Immunology,
                     Univ. of Colorado Hlth. Sci. Center, Campus Box B164, 4200
                     East Ninth Avenue, Denver, CO 80262, United States.
                     stephen.dreskin@uchsc.edu
SOURCE:              Immunology and Allergy Clinics of North America, (2004)
                     24/2 (141-162).
                     Refs: 157
                     ISSN: 0889-8561  CODEN: INCAEP
COUNTRY:             United States
DOCUMENT TYPE:       Journal; General Review
FILE SEGMENT:        013     Dermatology and Venereology
                     026     Immunology, Serology and Transplantation
```

Only hits not found in HCAPLUS are displayed

030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
CT Medical Descriptors:
*urticaria: CO, complication
*urticaria: DR, drug resistance
*urticaria: DT, drug therapy
*urticaria: ET, etiology
*urticaria: SI, side effect
*angioneurotic edema: SI, side effect
*chronic urticaria: DR, drug resistance
*chronic urticaria: DT, drug therapy
systemic disease
physical examination
medical specialist
pathogenicity
side effect: SI, side effect
anaphylaxis: SI, side effect
disease exacerbation: SI, side effect
drug safety
drug efficacy
drug megadose
drug tolerability
low drug dose
drug potency
sedation
increased appetite: SI, side effect
weight gain
human
clinical trial
meta analysis
review
priority journal
Drug Descriptors:
immunosuppressive agent: AE, adverse drug reaction
adrenalin
opiate: AE, adverse drug reaction
opiate: PD, pharmacology
vancomycin: AE, adverse drug reaction
vancomycin: PD, pharmacology
contrast medium: AE, adverse drug reaction
dipeptidyl carboxypeptidase inhibitor: AE, adverse drug reaction
nonsteroid antiinflammatory agent: AE, adverse drug reaction
acetylsalicylic acid: AE, adverse drug reaction
cyclooxygenase 2 inhibitor: AE, adverse drug reaction
cyclooxygenase 2 inhibitor: DT, drug therapy
beta adrenergic receptor blocking agent: AE, adverse drug reaction
antihypertensive agent: AE, adverse drug reaction
antiglaucoma agent: AE, adverse drug reaction
hydroxychloroquine
salazosulfapyridine
dapsone
doxepin: AE, adverse drug reaction
doxepin: CM, drug comparison
doxepin: DO, drug dose
doxepin: PD, pharmacology
zileuton: CM, drug comparison
leukotriene receptor blocking agent: AE, adverse drug reaction

leukotriene receptor blocking agent: CT, clinical trial
leukotriene receptor blocking agent: DO, drug dose
leukotriene receptor blocking agent: DT, drug therapy
leukotriene receptor blocking agent: PD, pharmacology
zafirlukast: CM, drug comparison
steroid: AE, adverse drug reaction
steroid: DO, drug dose
antihistaminic agent: AE, adverse drug reaction
antihistaminic agent: CT, clinical trial
antihistaminic agent: CB, drug combination
antihistaminic agent: DO, drug dose
antihistaminic agent: DT, drug therapy
antihistaminic agent: PD, pharmacology
cyclosporin A: AE, adverse drug reaction
cyclosporin A: CT, clinical trial
cyclosporin A: DT, drug therapy
cyclosporin A: PD, pharmacology
adrenergic receptor stimulating agent
calcium channel blocking agent
colchicine
methotrexate
gold: IM, intramuscular drug administration
capsaicin
warfarin
unindexed drug
cyproheptadine
fexofenadine
cimetidine
ranitidine

RN (adrenalin) 51-43-4, 55-31-2, 6912-68-1; (opiate) 53663-61-9, 8002-76-4, 8008-60-4; (vancomycin) 1404-90-6, 1404-93-9; (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (hydroxychloroquine) 118-42-3, 525-31-5; (salazosulfapyridine) 599-79-1; (dapsone) 80-08-0; (doxepin) 1229-29-4, 1668-19-5; (zileuton) **111406-87-2**, 132880-11-6; (zafirlukast) 107753-78-6; (**cyclosporin** A) **59865-13-3**, **63798-73-2**; (colchicine) 64-86-8; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (gold) 7440-57-5; (capsaicin) 404-86-4; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2; (cyproheptadine) 129-03-3, 969-33-5; (fexofenadine) 138452-21-8; (cimetidine) 51481-61-9, 70059-30-2; (ranitidine) 66357-35-5, 66357-59-3

CN ASA; Periactin; Allegra; Tagamet; Zantac; Zyflo

AB Persistent or frequent episodes of urticaria are difficult to evaluate and treat. The best test to identify most patients with a specific underlying cause (eg, physical trigger, allergen, systemic disease) likely is the taking of a careful and detailed history and performance of a physical examination by a specialist who is knowledgeable in urticarial disease. Further study of the pathogenesis and treatment of urticaria is crucial. Given the limited efficacy of presently approved antihistamine treatments and the significant side effects of steroids and **cyclosporine**, there is a pressing need to evaluate other anecdotally supported urticaria treatments in randomized controlled trials.

=> d ibib hitind abs 52-
YOU HAVE REQUESTED DATA FROM 19 ANSWERS - CONTINUE? Y/(N):y

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on STN
ACCESSION NUMBER: 2003165839 EMBASE

TITLE: Current drug therapy for rheumatoid arthritis.
AUTHOR: Kawai S.
CORPORATE SOURCE: S. Kawai, Institute of Medical Science, St. Marianna Univ. Sch. of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki 216-8512, Japan
SOURCE: Journal of Orthopaedic Science, (2003) 8/2 (259-263).
Refs: 29
ISSN: 0949-2658 CODEN: JOSCFS
COUNTRY: Japan
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
031 Arthritis and Rheumatism
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
CT Medical Descriptors:
*rheumatoid arthritis: DT, drug therapy
*rheumatoid arthritis: ET, etiology
gastrointestinal symptom: SI, side effect
heart infarction: SI, side effect
osteoporosis: SI, side effect
tuberculosis
quality of life
edema: SI, side effect
hypertension: SI, side effect
antiinflammatory activity
drug delivery system
human
nonhuman
clinical trial
conference paper
Drug Descriptors:
***cyclooxygenase 2 inhibitor: AE, adverse drug reaction**
***cyclooxygenase 2 inhibitor: DT, drug therapy**
***cyclooxygenase 2 inhibitor: PD, pharmacology**
*nonsteroid antiinflammatory agent: AE, adverse drug reaction
*nonsteroid antiinflammatory agent: DT, drug therapy
*nonsteroid antiinflammatory agent: PD, pharmacology
*glucocorticoid: AE, adverse drug reaction
*glucocorticoid: CT, clinical trial
***glucocorticoid: CB, drug combination**
*glucocorticoid: DO, drug dose
*glucocorticoid: DT, drug therapy
*glucocorticoid: PD, pharmacology
***antirheumatic agent: CB, drug combination**
*antirheumatic agent: DT, drug therapy
*antirheumatic agent: PD, pharmacology
arachidonic acid: EC, endogenous compound
prostaglandin synthase: EC, endogenous compound
cyclooxygenase 2: EC, endogenous compound
methotrexate: CT, clinical trial
methotrexate: CB, drug combination
methotrexate: CM, drug comparison
methotrexate: DO, drug dose
methotrexate: DT, drug therapy
salazosulfapyridine: DO, drug dose
salazosulfapyridine: DT, drug therapy
leflunomide: DT, drug therapy

etanercept: CT, clinical trial
etanercept: CM, drug comparison
etanercept: DT, drug therapy
infliximab: CT, clinical trial
infliximab: CB, drug combination
infliximab: CM, drug comparison
infliximab: DT, drug therapy
acetylsalicylic acid: DT, drug therapy
acetylsalicylic acid: PD, pharmacology
celecoxib: DT, drug therapy
celecoxib: PD, pharmacology
rofecoxib: DT, drug therapy
etodolac: DT, drug therapy
meloxicam: DT, drug therapy
prednisolone: CT, clinical trial
prednisolone: DO, drug dose
prednisolone: DT, drug therapy
etidronic acid: CT, clinical trial
etidronic acid: CB, drug combination
etidronic acid: DT, drug therapy
alendronic acid: CT, clinical trial
alendronic acid: CB, drug combination
alendronic acid: DT, drug therapy
risedronic acid: CT, clinical trial
risedronic acid: CB, drug combination
risedronic acid: DT, drug therapy
azathioprine: DT, drug therapy
azathioprine: PD, pharmacology
cyclophosphamide: DT, drug therapy
cyclophosphamide: PD, pharmacology
cyclosporin: DT, drug therapy
tsukubaenolide: CT, clinical trial
tsukubaenolide: DT, drug therapy
recombinant interleukin 1 receptor blocking agent: DT, drug therapy
diclofenac: PD, pharmacology
indometacin: PD, pharmacology
gold: DT, drug therapy
unindexed drug

RN (arachidonic acid) 506-32-1, 6610-25-9, 7771-44-0; (prostaglandin synthase) **39391-18-9**, **59763-19-8**, 9055-65-6; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (salazosulfapyridine) 599-79-1; (leflunomide) 75706-12-6; (etanercept) 185243-69-0, 200013-86-1; (infliximab) 170277-31-3; (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (celecoxib) 169590-42-5; (rofecoxib) **162011-90-7**, **186912-82-3**; (etodolac) 41340-25-4; (meloxicam) **71125-38-7**; (prednisolone) 50-24-8; (etidronic acid) 2809-21-4, 3794-83-0, 58449-82-4, 7414-83-7; (alendronic acid) 66376-36-1; (risedronic acid) 105462-24-6, 122458-82-6; (azathioprine) 446-86-6; (cyclophosphamide) 50-18-0; (**cyclosporin**) **79217-60-0**; (tsukubaenolide) 104987-11-3; (diclofenac) 15307-79-6, 15307-86-5; (indometacin) 53-86-1, 74252-25-8, 7681-54-1; (gold) 7440-57-5

CN Fk 506

CO Bayer (Germany)

AB The etiology of rheumatoid arthritis (RA) remains unclear at present, but advances have been made in the drug therapy for RA. Recent attention has been focused on selective **cyclooxygenase**-2 (**COX-2**) **inhibitors**, nonsteroidal antiinflammatory drugs (NSAIDs) that **inhibit** a subtype of **cyclooxygenase**. Various clinical studies have confirmed that the selective **COX-**

2 inhibitors cause fewer severe gastrointestinal complications, although an increased incidence of myocardial infarction was suggested. Terminal enzymes of the arachidonic acid cascade, such as membrane-associated prostaglandin E synthase, might be a target for new NSAIDs in the near future. Low-dose glucocorticoid treatment for RA has been reconsidered possibly to prevent articular destruction of RA. Special attention for glucocorticoid-induced osteoporosis by concomitant administration of bisphosphonates might be necessary. Disease-modifying antirheumatic drugs should be effective in delaying the progression of joint destruction and physical disability. Methotrexate, sulfasalazine, and leflunomide have shown such an effect. Inhibition of articular destruction was also proven by administration of the biologic agents etanercept and infliximab plus methotrexate. Tuberculosis complicated with infliximab therapy is one of the most important concerns in Japan. Agents that improve the quality of life of patients with RA are still needed.

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ACCESSION NUMBER: 2003245898 EMBASE
TITLE: [Kidney involvement in rheumatoid arthritis].
COINVOLGIMENTO RENALE IN CORSO DI ARTRITE REUMATOIDE.
AUTHOR: Icardi A.; Araghi P.; Ciabattoni M.; Romano U.; Lazzarini P.; Bianchi G.
CORPORATE SOURCE: Dr. A. Icardi, Unita Operativa Nefrologia Dialisi, DIMP - Ospedale La Colletta, Via del Giappone 5, 16011 Arenzano (Genova), Italy. andrea.icardi.usl3@libero.it
SOURCE: Reumatismo, (2003) 55/2 (76-85).
Refs: 80
ISSN: 0048-7449 CODEN: REUMEH
COUNTRY: Italy
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 028 Urology and Nephrology
031 Arthritis and Rheumatism
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: Italian
SUMMARY LANGUAGE: English; Italian
CT Medical Descriptors:
*kidney
*rheumatoid arthritis: DT, drug therapy
kidney biopsy
glomerulonephritis: CO, complication
glomerulonephritis: DI, diagnosis
kidney amyloidosis: CO, complication
kidney amyloidosis: DI, diagnosis
nephrotoxicity: SI, side effect
kidney injury: CO, complication
kidney injury: DI, diagnosis
kidney disease: CO, complication
kidney disease: DI, diagnosis
survival
morbidity
kidney failure: CO, complication
kidney failure: DT, drug therapy
kidney failure: TH, therapy
disease association
minimal change glomerulonephritis: CO, complication
minimal change glomerulonephritis: DI, diagnosis
dialysis
human

review
Drug Descriptors:
antirheumatic agent: AE, adverse drug reaction
antirheumatic agent: CB, drug combination
antirheumatic agent: DT, drug therapy
immunosuppressive agent: CB, drug combination
immunosuppressive agent: DT, drug therapy
nonsteroid antiinflammatory agent: AE, adverse drug reaction
nonsteroid antiinflammatory agent: DT, drug therapy
gold derivative: AE, adverse drug reaction
gold derivative: DT, drug therapy
penicillamine: AE, adverse drug reaction
penicillamine: DT, drug therapy
cyclosporin A: AE, adverse drug reaction
cyclosporin A: DT, drug therapy
methotrexate: AE, adverse drug reaction
methotrexate: DT, drug therapy
immunoglobulin A: EC, endogenous compound
leflunomide: AE, adverse drug reaction
leflunomide: DT, drug therapy
etanercept: AE, adverse drug reaction
etanercept: DT, drug therapy
neutrophil cytoplasmic antibody: EC, endogenous compound
amyloid A protein: EC, endogenous compound
interleukin 1: EC, endogenous compound
prostaglandin synthase: EC, endogenous compound
dipeptidyl carboxypeptidase inhibitor
diuretic agent
beta adrenergic receptor blocking agent
vasopressin: EC, endogenous compound
renin: EC, endogenous compound
angiotensin: EC, endogenous compound
aldosterone: EC, endogenous compound
paracetamol
rofecoxib: DT, drug therapy
celecoxib: DT, drug therapy
HLA DR3 antigen: EC, endogenous compound
HLA DQ antigen: EC, endogenous compound
HLA DR5 antigen: EC, endogenous compound
interleukin 2: EC, endogenous compound
cytochrome P450: EC, endogenous compound
unindexed drug

RN (penicillamine) 2219-30-9, 52-67-5; (**cyclosporin** A) **59865-13-3**, **63798-73-2**; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (leflunomide) 75706-12-6; (etanercept) 185243-69-0, 200013-86-1; (amyloid A protein) 59165-71-8; (prostaglandin synthase) **39391-18-9**, **59763-19-8**, 9055-65-6; (vasopressin) 11000-17-2; (renin) 61506-93-2, 9015-94-5; (angiotensin) 11128-99-7, 1407-47-2; (aldosterone) 52-39-1, 6251-69-0; (paracetamol) 103-90-2; (rofecoxib) **162011-90-7**, **186912-82-3**; (celecoxib) 169590-42-5; (interleukin 2) 85898-30-2; (cytochrome P450) 9035-51-2

AB Rheumatoid Arthritis (RA) is a widespread disease and its renal involvement, relatively common, is clinically significant because worsens course and mortality of the primary disease. There is still no agreement on the prevalence of renal disorders in RA: data analysis originates from different sources, as death certificates, autopsies, clinical and laboratory findings and kidney biopsies, each with its limitations. Histoimmunological studies on bioptical specimens of patients with RA and kidney damage, led to clarify prevalent pathologies. In order of frequency: glomerulonephritis and amyloidosis (60-65% and 20-30%

respectively), followed by acute or chronic interstitial nephritis. Kidney injury during RA includes secondary renal amyloidosis, nephrotoxic effects of antirheumatic drugs and nephropathies as extra-articular manifestations (rheumatoid nephropathy). Amyloidosis affects survival, increases morbidity and is the main cause of end stage renal disease in patients with RA and nephropathy. Strong association between RA activity and amyloidosis needs the use of immunosuppressive and combined therapies, to prevent this complication and reduce risk of dialysis. Long-lasting and combined RA pharmacotherapy involves various renal side effects. In this review we describe NSAIDs and DMARDs (Disease-Modifying Antirheumatic Drugs) nephrotoxicity, particularly by gold compounds, D-penicillamine, **cyclosporine** A and methotrexate. Rare cases of IgA glomerulonephritis during immunomodulating therapy with leflunomide and TNF blocking receptor (etanercept) are reported; real clinical significance of this drug-related nephropathy will be established by development of RA treatment. In RA nephropathies, mesangial glomerulonephritis is the most frequent histological lesion (35-60 % out of biopsies from patients with urinary abnormalities and/or kidney impairment), followed by minimal change glomerulopathy (3-14%) and p-ANCA positive necrotizing crescentic glomerulonephritis.

L203 ANSWER 54 OF 70 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002432577 EMBASE
TITLE: Do non-steroidal anti-inflammatory drugs and **COX-2** selective **inhibitors** have different renal effects?.
AUTHOR: Galli G.; Panzetta G.
CORPORATE SOURCE: Dr. G. Galli, U.O. Nefrologia e Dialisi, Via G. Stuparich 1, 34125 Trieste, Italy. giovanni.galli@aots.sanita.fvg.it
SOURCE: Journal of Nephrology, (2002) 15/5 (480-488).
Refs: 76
ISSN: 1121-8428 CODEN: JLNEEL
COUNTRY: Italy
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 028 Urology and Nephrology
037 Drug Literature Index
030 Pharmacology
038 Adverse Reactions Titles
018 Cardiovascular Diseases and Cardiovascular Surgery
031 Arthritis and Rheumatism
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
CT Medical Descriptors:
*acute kidney failure: SI, side effect
human
clinical trial
nonhuman
drug effect
drug mechanism
enzyme inhibition
prostaglandin synthesis
nephrotoxicity: SI, side effect
kidney circulation
kidney blood flow
vasodilatation
renin release
sodium urine level
diuresis

vasoconstriction
glomerulus filtration
tissue injury
kidney perfusion
disease predisposition
kidney papilla necrosis: SI, side effect
interstitial nephritis: SI, side effect
glomerulonephritis: SI, side effect
membranous glomerulonephritis: SI, side effect
focal glomerulosclerosis: SI, side effect
hyperkalemia: SI, side effect
hypertension: SI, side effect
hypertension: DT, drug therapy
drug safety
aged
arthritis: DT, drug therapy
dyspnea: SI, side effect
ankle edema: SI, side effect
ankle edema: DT, drug therapy
drug withdrawal
drug efficacy
Bartter syndrome: DT, drug therapy
proteinuria: SI, side effect
eosinophilia: SI, side effect
eosinophiluria: SI, side effect
hyponatremia: SI, side effect
hyponatremia: DT, drug therapy
drug antagonism
drug potentiation
kidney tumor: DT, drug therapy
protein expression
kidney fibrosis: SI, side effect
heart disease: DT, drug therapy
disease exacerbation: SI, side effect
kidney dysfunction: SI, side effect
review
Drug Descriptors:
*nonsteroid antiinflammatory agent: DT, drug therapy
*nonsteroid antiinflammatory agent: CM, drug comparison
*nonsteroid antiinflammatory agent: PD, pharmacology
*nonsteroid antiinflammatory agent: AE, adverse drug reaction
***nonsteroid antiinflammatory agent: CB, drug combination**
***nonsteroid antiinflammatory agent: IT, drug interaction**
*nonsteroid antiinflammatory agent: CT, clinical trial
***cyclooxygenase 2 inhibitor: DT, drug therapy**
***cyclooxygenase 2 inhibitor: CM, drug comparison**
***cyclooxygenase 2 inhibitor: PD, pharmacology**
***cyclooxygenase 2 inhibitor: AE, adverse drug reaction**
***cyclooxygenase 2 inhibitor: CT, clinical trial**
***cyclooxygenase 2 inhibitor: CB, drug combination**
***cyclooxygenase 2 inhibitor: PO, oral drug administration**
prostaglandin synthase: EC, endogenous compound
prostaglandin: EC, endogenous compound
renin: EC, endogenous compound
sodium: EC, endogenous compound
cyclooxygenase 1: EC, endogenous compound
cyclooxygenase 2: EC, endogenous compound
rofecoxib: DT, drug therapy
rofecoxib: CM, drug comparison
rofecoxib: PD, pharmacology

rofecoxib: AE, adverse drug reaction
rofecoxib: CT, clinical trial
celecoxib: DT, drug therapy
celecoxib: CM, drug comparison
celecoxib: PD, pharmacology
celecoxib: AE, adverse drug reaction
celecoxib: CT, clinical trial
celecoxib: CB, drug combination
celecoxib: PO, oral drug administration
acetylsalicylic acid: DT, drug therapy
acetylsalicylic acid: CB, drug combination
acetylsalicylic acid: AE, adverse drug reaction
diuretic agent: DT, drug therapy
diuretic agent: CB, drug combination
diuretic agent: IT, drug interaction
diuretic agent: PD, pharmacology
beta adrenergic receptor blocking agent: DT, drug therapy
beta adrenergic receptor blocking agent: PD, pharmacology
dipeptidyl carboxypeptidase inhibitor: DT, drug therapy
dipeptidyl carboxypeptidase inhibitor: CB, drug combination
dipeptidyl carboxypeptidase inhibitor: IT, drug interaction
dipeptidyl carboxypeptidase inhibitor: AE, adverse drug reaction
calcium channel blocking agent: DT, drug therapy
clonidine: DT, drug therapy
vasodilator agent: DT, drug therapy
ketorolac: DT, drug therapy
ketorolac: PD, pharmacology
ketorolac: AE, adverse drug reaction
ketorolac: CM, drug comparison
ketorolac: CT, clinical trial
indometacin: DT, drug therapy
indometacin: PD, pharmacology
indometacin: CM, drug comparison
indometacin: CT, clinical trial
indometacin: AE, adverse drug reaction
naproxen: DT, drug therapy
naproxen: PD, pharmacology
naproxen: CM, drug comparison
naproxen: CT, clinical trial
naproxen: AE, adverse drug reaction
nimesulide: DT, drug therapy
nimesulide: PD, pharmacology
nimesulide: CM, drug comparison
nimesulide: CT, clinical trial
nimesulide: AE, adverse drug reaction
cyclosporin: DT, drug therapy
creatinine: EC, endogenous compound

RN (prostaglandin synthase) **39391-18-9**, **59763-19-8**, 9055-65-6; (renin) 61506-93-2, 9015-94-5; (sodium) 7440-23-5; (rofecoxib) **162011-90-7**, **186912-82-3**; (celecoxib) 169590-42-5; (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (clonidine) 4205-90-7, 4205-91-8, 57066-25-8; (ketorolac) 74103-06-3; (indometacin) 53-86-1, 74252-25-8, 7681-54-1; (naproxen) 22204-53-1, 26159-34-2; (nimesulide) 51803-78-2; (**cyclosporin**) **79217-60-0**; (creatinine) 19230-81-0, 60-27-5

AB The main mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs) is the **inhibition** of **cyclooxygenase** (COX), the enzyme involved in prostaglandin synthesis. NSAID nephrotoxicity is linked to this, since prostaglandins act not only in response to inflammatory stimuli, but also as modulators of physiological functions.

When blood volume is compromised, prostaglandins play a role in the renal circulation including vasodilatation, renin secretion, and sodium and water excretion. If vasoconstrictive forces stimulated to maintain the filtration fraction are not balanced by prostaglandin-induced vasodilatation, renal failure may occur. The identification of two isoforms of COX (COX-1 or the "constitutive" isoform and COX-2 or the "inducible" isoform) led to the hypothesis that COX-1-derived prostaglandins were involved in regulating physiological functions, whereas COX-2-derived prostaglandins played a major role in inflammation or tissue damage. It was assumed that the pharmacological effects of NSAIDs depend on the **inhibition** of **COX-2**, whereas the toxic organ-specific effects are linked to the inhibition of COX-1. Therefore, rofecoxib and celecoxib, selective **inhibitors** of **COX-2**, at least in vitro, were introduced. However, COX-2 plays a physiological role in many tissues and organs, and COX-1 is also involved in inflammatory reactions. In the kidney, "constitutive" expression has been demonstrated for both isoforms. **COX-2 inhibitor** drugs, such as NSAIDs, reduce sodium excretion, and may cause acute renal failure in patients in whom the maintenance of adequate renal perfusion is "prostaglandin-dependent". Therefore, **COX-2 inhibitors**, like other NSAIDs, must be used cautiously or not at all in patients with predisposing diseases.

L203 ANSWER 55 OF 70 EMBASE
on STN

ACCESSION NUMBER: 2002371418 EMBASE
TITLE: Proton pump inhibitors: Gastrointestinal indications and beyond.
AUTHOR: Arvanitakis C.; Blum A.
CORPORATE SOURCE: Dr. C. Arvanitakis, Fourth Department of Medicine, Hippocration General Hospital, University of Thessaloniki, Konstantinoupoleos 49, S46 42 Thessaloniki, Greece. carvanit@med.auth.gr
SOURCE: European Journal of Gastroenterology and Hepatology, (1 Sep 2002) 14/SUPPL. 1 (S3-S4).
ISSN: 0954-691X CODEN: EJGHES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
CT Medical Descriptors:
*gastroesophageal reflux: DT, drug therapy
*gastroesophageal reflux: PC, prevention
*gastroduodenal ulcer: DT, drug therapy
*gastroduodenal ulcer: PC, prevention
Helicobacter pylori
Helicobacter infection: DT, drug therapy
eradication therapy
drug safety
drug efficacy
cancer control
gastrointestinal toxicity: DT, drug therapy
gastrointestinal toxicity: SI, side effect
drug indication
hemodialysis patient
cancer patient
kidney graft

human
conference paper
priority journal
Drug Descriptors:
*proton pump inhibitor: AE, adverse drug reaction
***proton pump inhibitor: CB, drug combination**
*proton pump inhibitor: IT, drug interaction
*proton pump inhibitor: DT, drug therapy
rabeprazole: AE, adverse drug reaction
rabeprazole: DT, drug therapy
esomeprazole: AE, adverse drug reaction
esomeprazole: DT, drug therapy
antibiotic agent: CB, drug combination
antibiotic agent: DT, drug therapy
immunosuppressive agent: IT, drug interaction
cyclosporin: IT, drug interaction
tsukubaenolide: IT, drug interaction
nonsteroid antiinflammatory agent: AE, adverse drug reaction
prostaglandin synthase: EC, endogenous compound
cyclooxygenase 1: EC, endogenous compound
cyclooxygenase 2: EC, endogenous compound
prostaglandin: EC, endogenous compound
cyclooxygenase 2 inhibitor: AE, adverse drug reaction
cyclooxygenase 2 inhibitor: DT, drug therapy
RN (rabeprazole) 117976-89-3, 117976-90-6; (esomeprazole) 119141-88-7, 202742-32-3, 217087-09-7, 217087-10-0; (**cyclosporin**) **79217-60-0**; (tsukubaenolide) 104987-11-3; (prostaglandin synthase) **39391-18-9**, **59763-19-8**, 9055-65-6

L203 ANSWER 56 OF 70 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2001217102 EMBASE
TITLE: Rheumatoid arthritis: Guidelines for emerging therapies.
AUTHOR: Blumberg S.N.; Fox D.A.
CORPORATE SOURCE: Dr. S.N. Blumberg, Gralyn Health Associates Inc., PO Box 2634, Farmington Hills, MI 48333, United States. snblumberg@msn.com
SOURCE: American Journal of Managed Care, (2001) 7/6 (617-626). Refs: 47
ISSN: 1088-0224 CODEN: AJMCFY
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 031 Arthritis and Rheumatism
037 Drug Literature Index
017 Public Health, Social Medicine and Epidemiology
036 Health Policy, Economics and Management
022 Human Genetics
038 Adverse Reactions Titles
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
030 Pharmacology
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
CT Medical Descriptors:
*rheumatoid arthritis: EP, epidemiology
*rheumatoid arthritis: ET, etiology
*rheumatoid arthritis: DT, drug therapy
*rheumatoid arthritis: DM, disease management
*practice guideline

human
meta analysis
clinical trial
drug use
joint destruction
disability
managed care organization
economic evaluation
model
prevalence
incidence
pathogenesis
genetic analysis
disease severity
health care cost
disease classification
symptomatology
disease course
prognosis
disease activity
prescription
drug efficacy
gastrointestinal symptom: SI, side effect
protein synthesis inhibition
metabolic disorder: SI, side effect
retina disease: SI, side effect
monotherapy
leukopenia: SI, side effect
autoimmune disease: SI, side effect
kidney disease: SI, side effect
hypertension: SI, side effect
immune response
hypersensitivity reaction: SI, side effect
injection site
dose response
physician attitude
clinical practice
drug cost
treatment outcome
review
priority journal
Drug Descriptors:
*antirheumatic agent: DT, drug therapy
*antirheumatic agent: PE, pharmacoeconomics
*antirheumatic agent: PD, pharmacology
*antirheumatic agent: AE, adverse drug reaction
*antirheumatic agent: DO, drug dose
*antirheumatic agent: AR, intraarticular drug administration
*antirheumatic agent: AD, drug administration
***antirheumatic agent: CB, drug combination**
*antirheumatic agent: CT, clinical trial
*antirheumatic agent: CM, drug comparison
*antirheumatic agent: PO, oral drug administration
antiinflammatory agent: DT, drug therapy
antiinflammatory agent: PE, pharmacoeconomics
antiinflammatory agent: PD, pharmacology
antiinflammatory agent: AE, adverse drug reaction
antiinflammatory agent: DO, drug dose
antiinflammatory agent: AR, intraarticular drug administration
antiinflammatory agent: AD, drug administration

antiinflammatory agent: CT, clinical trial
tumor necrosis factor antibody: DT, drug therapy
tumor necrosis factor antibody: PD, pharmacology
tumor necrosis factor antibody: CT, clinical trial
tumor necrosis factor antibody: CB, drug combination
tumor necrosis factor antibody: AE, adverse drug reaction
tumor necrosis factor antibody: PE, pharmacoeconomics
nonsteroid antiinflammatory agent: DT, drug therapy
nonsteroid antiinflammatory agent: PE, pharmacoeconomics
nonsteroid antiinflammatory agent: PD, pharmacology
nonsteroid antiinflammatory agent: AE, adverse drug reaction
nonsteroid antiinflammatory agent: DO, drug dose
nonsteroid antiinflammatory agent: AR, intraarticular drug administration
nonsteroid antiinflammatory agent: AD, drug administration
nonsteroid antiinflammatory agent: CT, clinical trial
rheumatoid factor: EC, endogenous compound
prostaglandin synthase: EC, endogenous compound
celecoxib: DT, drug therapy
celecoxib: PD, pharmacology
celecoxib: AE, adverse drug reaction
celecoxib: CT, clinical trial
rofecoxib: DT, drug therapy
rofecoxib: PD, pharmacology
rofecoxib: AE, adverse drug reaction
rofecoxib: CT, clinical trial
corticosteroid: DT, drug therapy
corticosteroid: DO, drug dose
corticosteroid: AE, adverse drug reaction
corticosteroid: AR, intraarticular drug administration
corticosteroid: AD, drug administration
corticosteroid: PD, pharmacology
corticosteroid: CT, clinical trial
prednisone: DT, drug therapy
methylprednisolone: DT, drug therapy
glucocorticoid: DT, drug therapy
glucocorticoid: PD, pharmacology
glucocorticoid: AE, adverse drug reaction
glucocorticoid: CT, clinical trial
hydroxychloroquine sulfate: DT, drug therapy
hydroxychloroquine sulfate: PD, pharmacology
hydroxychloroquine sulfate: CB, drug combination
hydroxychloroquine sulfate: AE, adverse drug reaction
hydroxychloroquine sulfate: CT, clinical trial
hydroxychloroquine sulfate: CM, drug comparison
hydroxychloroquine sulfate: PE, pharmacoeconomics
salazosulfapyridine: DT, drug therapy
salazosulfapyridine: PD, pharmacology
salazosulfapyridine: AE, adverse drug reaction
salazosulfapyridine: CT, clinical trial
salazosulfapyridine: CB, drug combination
salazosulfapyridine: CM, drug comparison
salazosulfapyridine: PE, pharmacoeconomics
methotrexate: DT, drug therapy
methotrexate: PD, pharmacology
methotrexate: CT, clinical trial
methotrexate: CM, drug comparison
methotrexate: AE, adverse drug reaction
methotrexate: CB, drug combination
methotrexate: PE, pharmacoeconomics
leflunomide: DT, drug therapy

leflunomide: PD, pharmacology
leflunomide: CB, drug combination
leflunomide: AE, adverse drug reaction
leflunomide: PE, pharmacoeconomics
penicillamine: DT, drug therapy
penicillamine: PD, pharmacology
penicillamine: AE, adverse drug reaction
cyclosporin A: DT, drug therapy
cyclosporin A: PD, pharmacology
cyclosporin A: CB, drug combination
cyclosporin A: AE, adverse drug reaction
cyclosporin A: CT, clinical trial
gold salt: DT, drug therapy
gold salt: AE, adverse drug reaction
gold salt: PE, pharmacoeconomics
auranofin: DT, drug therapy
auranofin: PO, oral drug administration
auranofin: PD, pharmacology
cytokine: EC, endogenous compound
tumor necrosis factor: EC, endogenous compound
infliximab: DT, drug therapy
infliximab: PD, pharmacology
infliximab: CT, clinical trial
infliximab: CB, drug combination
infliximab: AE, adverse drug reaction
infliximab: PE, pharmacoeconomics
etanercept: DT, drug therapy
etanercept: PD, pharmacology
etanercept: CT, clinical trial
etanercept: CB, drug combination
etanercept: AE, adverse drug reaction
placebo
aurothioglucose: DT, drug therapy
aurothioglucose: AE, adverse drug reaction
aurothioglucose: PE, pharmacoeconomics
tumor necrosis factor receptor: EC, endogenous compound
interleukin 10: EC, endogenous compound
interleukin 1: EC, endogenous compound
unindexed drug
hydroxychloroquine

RN (tumor necrosis factor antibody) 162774-06-3; (rheumatoid factor) 9009-79-4; (prostaglandin synthase) **39391-18-9**, **59763-19-8**, 9055-65-6; (celecoxib) 169590-42-5; (rofecoxib) **162011-90-7**, **186912-82-3**; (prednisone) 53-03-2; (methylprednisolone) 6923-42-8, 83-43-2; (hydroxychloroquine sulfate) 747-36-4; (salazosulfapyridine) 599-79-1; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (leflunomide) 75706-12-6; (penicillamine) 2219-30-9, 52-67-5; (**cyclosporin** A) **59865-13-3**, **63798-73-2**; (auranofin) 34031-32-8; (infliximab) 170277-31-3; (etanercept) 185243-69-0, 200013-86-1; (aurothioglucose) 12192-57-3; (hydroxychloroquine) 118-42-3, 525-31-5

CN Neoral; Solganal; Azulfidine; Rheumatrex; Plaquenil; Arava; Remicade

AB The individual and societal impacts of rheumatoid arthritis are of substantial consequence. Management of the disease has pharmacologically focused on the use of anti-inflammatories and disease-modifying antirheumatic drugs, which are only partially successful in retarding joint destruction and functional disability. The recent emergence of cytokine antagonists (anti-tumor necrosis factor therapy) challenges clinicians and managed care organizations with the need to develop new treatment guidelines. Recent developments in the understanding of

rheumatoid arthritis, including its epidemiological characteristics, economic costs, clinical progression, and current and emerging therapies, are reviewed. Pharmacologic utilization models are proposed. Pending the development of broad-based consensus treatment recommendations, interim treatment guidelines are suggested.

L203 ANSWER 57 OF 70 EMBASE
on STN

ACCESSION NUMBER: 2001087284 EMBASE
TITLE: New agents for the medical treatment of interstitial cystitis.
AUTHOR: Theoharides T.C.; Sant G.R.
CORPORATE SOURCE: T.C. Theoharides, Dept. of Pharmacology/Exp. Therap., Internal Medicine, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111, United States. theoharis.theoharides@tufts.edu
SOURCE: Expert Opinion on Investigational Drugs, (2001) 10/3 (521-546).
Refs: 234
ISSN: 1354-3784 CODEN: EOIDER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
CT Medical Descriptors:
*interstitial cystitis: DI, diagnosis
*interstitial cystitis: DT, drug therapy
bladder disease: DI, diagnosis
bladder disease: DT, drug therapy
clinical feature
chronic disease: DI, diagnosis
chronic disease: DT, drug therapy
prostatitis: DI, diagnosis
prostatitis: DT, drug therapy
prevalence
disease severity
symptomatology
bladder biopsy
disease exacerbation
mast cell
neurogenic inflammation: DI, diagnosis
neurogenic inflammation: DT, drug therapy
neuropathy
neurolysis
sensory nerve
sensory stimulation
cell protection
antiinflammatory activity
side effect: SI, side effect
human
nonhuman
male
female
mouse
major clinical study

controlled study
animal tissue
adolescent
child
adult
review
Drug Descriptors:
*glycosaminoglycan: EC, endogenous compound
*dimethyl sulfoxide: AE, adverse drug reaction
*dimethyl sulfoxide: DT, drug therapy
*dimethyl sulfoxide: PD, pharmacology
*dimethyl sulfoxide: VE, intravesical drug administration
*pentosan polysulfate: AE, adverse drug reaction
*pentosan polysulfate: DT, drug therapy
*pentosan polysulfate: PD, pharmacology
*pentosan polysulfate: PO, oral drug administration
gabapentin: AE, adverse drug reaction
gabapentin: DT, drug therapy
gabapentin: PD, pharmacology
mexiletine: AE, adverse drug reaction
mexiletine: DT, drug therapy
mexiletine: PD, pharmacology
pentazocine: AE, adverse drug reaction
pentazocine: DT, drug therapy
pentazocine: PD, pharmacology
prochlorperazine: AE, adverse drug reaction
prochlorperazine: DT, drug therapy
prochlorperazine: PD, pharmacology
propiram fumarate: AE, adverse drug reaction
propiram fumarate: DT, drug therapy
propiram fumarate: PD, pharmacology
propiram fumarate: PO, oral drug administration
tramadol: AE, adverse drug reaction
tramadol: DT, drug therapy
tramadol: PD, pharmacology
amitriptyline: AE, adverse drug reaction
amitriptyline: DT, drug therapy
amitriptyline: PD, pharmacology
desipramine: AE, adverse drug reaction
desipramine: DT, drug therapy
desipramine: PD, pharmacology
doxepin: AE, adverse drug reaction
doxepin: DT, drug therapy
doxepin: PD, pharmacology
imipramine: AE, adverse drug reaction
imipramine: DT, drug therapy
imipramine: PD, pharmacology
leuprorelin: AE, adverse drug reaction
leuprorelin: DT, drug therapy
leuprorelin: PD, pharmacology
tamoxifen: AE, adverse drug reaction
tamoxifen: DT, drug therapy
tamoxifen: PD, pharmacology
celecoxib: AE, adverse drug reaction
celecoxib: DT, drug therapy
celecoxib: PD, pharmacology
choline magnesium trisalicylate: AE, adverse drug reaction
choline magnesium trisalicylate: DT, drug therapy
choline magnesium trisalicylate: PD, pharmacology
chondroitin sulfate: AE, adverse drug reaction

chondroitin sulfate: CB, drug combination
chondroitin sulfate: DT, drug therapy
chondroitin sulfate: PD, pharmacology
quercetin: AE, adverse drug reaction
quercetin: CB, drug combination
quercetin: DT, drug therapy
quercetin: PD, pharmacology
dipyrone: AE, adverse drug reaction
dipyrone: DT, drug therapy
dipyrone: PD, pharmacology
rofecoxib: AE, adverse drug reaction
rofecoxib: DT, drug therapy
rofecoxib: PD, pharmacology
leukotriene receptor blocking agent: AE, adverse drug reaction
leukotriene receptor blocking agent: DT, drug therapy
leukotriene receptor blocking agent: PD, pharmacology
cyclosporin: AE, adverse drug reaction
cyclosporin: DT, drug therapy
cyclosporin: PD, pharmacology
etanercept: AE, adverse drug reaction
etanercept: DT, drug therapy
etanercept: PD, pharmacology
infliximab: AE, adverse drug reaction
infliximab: DT, drug therapy
infliximab: PD, pharmacology
methotrexate: AE, adverse drug reaction
methotrexate: DT, drug therapy
methotrexate: PD, pharmacology
cromoglycate disodium: AE, adverse drug reaction
cromoglycate disodium: DT, drug therapy
cromoglycate disodium: PD, pharmacology
hydroxyzine: AE, adverse drug reaction
hydroxyzine: DT, drug therapy
hydroxyzine: PD, pharmacology
suplatast tosylate: AE, adverse drug reaction
suplatast tosylate: DT, drug therapy
suplatast tosylate: PD, pharmacology
unindexed drug
mexitie
prochlorperazine maleate
sinepuan
tamoxifen citrate
algonot plus
montelukast
zafirlukast
zileuton
cyclosporin A
embrel
hydroxyzine embonate

RN (dimethyl sulfoxide) 67-68-5; (pentosan polysulfate) 116001-96-8, 37300-21-3, 37319-17-8; (gabapentin) 60142-96-3; (mexiletine) 31828-71-4, 5370-01-4; (pentazocine) 359-83-1, 64024-15-3; (prochlorperazine) 58-38-8; (propiram fumarate) 13717-04-9; (tramadol) 27203-92-5, 36282-47-0; (amitriptyline) 50-48-6, 549-18-8; (desipramine) 50-47-5, 58-28-6; (doxepin) 1229-29-4, 1668-19-5; (imipramine) 113-52-0, 50-49-7; (leuprorelin) 53714-56-0, 74381-53-6; (tamoxifen) 10540-29-1; (celecoxib) 169590-42-5; (choline magnesium trisalicylate) 64425-90-7; (chondroitin sulfate) 9007-28-7, 9082-07-9; (quercetin) 117-39-5; (dipyrone) 50567-35-6, 5907-38-0, 68-89-3; (rofecoxib) **162011-90-7**, **186912-82-3**; (**cyclosporin**) **79217-60-0**;

(etanercept) 185243-69-0, 200013-86-1; (infliximab) 170277-31-3; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (cromoglycate disodium) 15826-37-6, 16110-51-3, 93356-79-7, 93356-84-4; (hydroxyzine) 2192-20-3, 64095-02-9, 68-88-2; (suplatast tosylate) 94055-76-2; (prochlorperazine maleate) 84-02-6; (tamoxifen citrate) 54965-24-1; (montelukast) 151767-02-1, 158966-92-8; (zafirlukast) 107753-78-6; (zileuton) **111406-87-2**, 132880-11-6; (**cyclosporin** A) **59865-13-3**, **63798-73-2**; (hydroxyzine embonate) 10246-75-0

CN Neurontin; Mexitie; Talwin; Compazine; Dirame; Ultram; Elavil; Norpramin; Sinepuan; Tofranil; Lupron; Nolvadex; Celebrex; Trilisate; Algonot plus; Novalgin; Vioxx; Singulair; Accolate; Zyflo; Neoral; Embrel; Remicade; Gastrocrom; Atarax; Vistaril; Ipd 1151t

AB Interstitial cystitis (IC) is a painful, sterile, disorder of the urinary bladder characterised by urgency, frequency, nocturia and pain. IC occurs primarily in women but also in men with recent findings indicating that chronic, abacterial prostatitis may be a variant of this condition. The prevalence of IC has ranged from about 8-60 cases/100,000 female patients depending on the population evaluated. About 10% of patients have severe symptoms that are associated with Hunner's ulcers on bladder biopsy; the rest could be grouped in those with or without bladder inflammation. Symptoms of IC are exacerbated by stress, certain foods and ovulatory hormones. Many patients also experience allergies, irritable bowel syndrome (IBS) and migraines. There have been various reports indicating dysfunction of the bladder glycosaminoglycan (GAG) protective layer and many publications showing a high number of activated bladder mast cells. Increasing evidence suggests that neurogenic inflammation and/or neuropathic pain is a major component of IC pathophysiology. Approved treatments so far include intravesical administration of dimethylsulphoxide (DMSO) or oral pentosanpolysulphate (PPS). New treatments focus on the combined use of drugs that modulate bladder sensory nerve stimulation (neurolytic agents), inhibit neurogenic activation of mast cells, or provide urothelial cytoprotection, together with new drugs with anti-inflammatory activity.

L203 ANSWER 58 OF 70 EMBASE
on STN

ACCESSION NUMBER: 2000354575 EMBASE
TITLE: Nonsteroidal anti-inflammatory drugs and opioids: Safety and usage concerns in the differential treatment of postoperative orofacial pain.
AUTHOR: Swift J.Q.
CORPORATE SOURCE: Dr. J.Q. Swift, 7-174 Moos Tower, 515 Delaware St South East, Minneapolis, MN 55455, United States. swift001@tc.umn.edu
SOURCE: Journal of Oral and Maxillofacial Surgery, (2000) 58/10 SUPPL. 2 (8-11).
Refs: 10
ISSN: 0278-2391 CODEN: JOMSDA
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 011 Otorhinolaryngology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

CT Medical Descriptors:
*postoperative pain: CO, complication
*postoperative pain: DT, drug therapy
*face pain: CO, complication
*face pain: DT, drug therapy

drug safety
surgical wound
gastrointestinal symptom: SI, side effect
kidney disease: SI, side effect
allergic reaction: SI, side effect
prostaglandin synthesis
cardiovascular disease: SI, side effect
central nervous system disease: SI, side effect
liver disease: SI, side effect
analgesia
drug dependence: SI, side effect
respiration depression: SI, side effect
urine retention: SI, side effect
drug antagonism
human
review
Drug Descriptors:
*nonsteroid antiinflammatory agent: AE, adverse drug reaction
***nonsteroid antiinflammatory agent: CB, drug combination**
*nonsteroid antiinflammatory agent: IT, drug interaction
*nonsteroid antiinflammatory agent: DT, drug therapy
*nonsteroid antiinflammatory agent: PO, oral drug administration
*opiate agonist: AE, adverse drug reaction
*opiate agonist: AD, drug administration
***opiate agonist: CB, drug combination**
*opiate agonist: DT, drug therapy
*opiate agonist: IM, intramuscular drug administration
*opiate agonist: NA, intranasal drug administration
*opiate agonist: IV, intravenous drug administration
*opiate agonist: PO, oral drug administration
*opiate agonist: PA, parenteral drug administration
*opiate agonist: DL, intradermal drug administration
***paracetamol: CB, drug combination**
*paracetamol: DT, drug therapy
*paracetamol: PO, oral drug administration
*antihypertensive agent: IT, drug interaction
prostaglandin: EC, endogenous compound
prostaglandin synthase: EC, endogenous compound
cyclooxygenase 2 inhibitor: EC, endogenous compound
thromboxane A2: EC, endogenous compound
opiate receptor: EC, endogenous compound
butorphanol tartrate: DT, drug therapy
butorphanol tartrate: NA, intranasal drug administration
dipeptidyl carboxypeptidase inhibitor: IT, drug interaction
beta adrenergic receptor blocking agent: IT, drug interaction
diuretic agent: IT, drug interaction
lithium: IT, drug interaction
digoxin: IT, drug interaction
cyclosporin: IT, drug interaction
anticoagulant agent: IT, drug interaction
alcohol: IT, drug interaction
methotrexate: IT, drug interaction
oral antidiabetic agent: IT, drug interaction
oral antidiabetic agent: PO, oral drug administration
anticonvulsive agent: IT, drug interaction
carbonate dehydratase inhibitor: IT, drug interaction
antidiarrheal agent: IT, drug interaction
barbituric acid derivative: IT, drug interaction
carbamazepine: IT, drug interaction
central depressant agent: IT, drug interaction

warfarin: IT, drug interaction
hydroxyzine: IT, drug interaction
hypnotic agent: IT, drug interaction
unindexed drug
acetylsalicylic acid
RN (paracetamol) 103-90-2; (prostaglandin synthase) **39391-18-9**, **59763-19-8**, 9055-65-6; (thromboxane A2) 57576-52-0; (butorphanol tartrate) 58786-99-5; (lithium) 7439-93-2; (digoxin) 20830-75-5, 57285-89-9; (**cyclosporin**) **79217-60-0**; (alcohol) 64-17-5; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (carbamazepine) 298-46-4, 8047-84-5; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2; (hydroxyzine) 2192-20-3, 64095-02-9, 68-88-2; (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1
CN (1) Stadol ns; Aspirin
CO (1) Bristol Myers Squibb (United States)

L203 ANSWER 59 OF 70 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002033436 EMBASE
TITLE: Rheumatoid arthritis in the geriatric patient.
AUTHOR: Marshall L.L.
CORPORATE SOURCE: L.L. Marshall, Mercer Univ. Southern Sch. of Pharm., Atlanta, GA 30341, United States
SOURCE: Journal of Geriatric Drug Therapy, (1999) 12/4 (45-72). Refs: 49
ISSN: 8756-4629 CODEN: JGDTEF
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 020 Gerontology and Geriatrics
031 Arthritis and Rheumatism
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
CT Medical Descriptors:
*rheumatoid arthritis: DT, drug therapy
*rheumatoid arthritis: TH, therapy
geriatric patient
autoimmune disease
cartilage degeneration
bone destruction
disease course
onset age
disease activity
daily life activity
risk benefit analysis
treatment planning
drug efficacy
exercise
diet therapy
liver toxicity: SI, side effect
gastrointestinal symptom: SI, side effect
rash: SI, side effect
stomatitis: SI, side effect
diarrhea: SI, side effect
photosensitivity: SI, side effect
Stevens Johnson syndrome: SI, side effect
bone marrow suppression: SI, side effect
thrombocytopenia: SI, side effect
human

clinical trial
review
Drug Descriptors:
*nonsteroid antiinflammatory agent: AE, adverse drug reaction
***nonsteroid antiinflammatory agent: CB, drug combination**
*nonsteroid antiinflammatory agent: DT, drug therapy
*antirheumatic agent: AE, adverse drug reaction
***antirheumatic agent: CB, drug combination**
*antirheumatic agent: DT, drug therapy
***cyclooxygenase 2 inhibitor: CT, clinical trial**
***cyclooxygenase 2 inhibitor: DT, drug therapy**
corticosteroid: AE, adverse drug reaction
corticosteroid: DT, drug therapy
corticosteroid: PO, oral drug administration
methotrexate: AE, adverse drug reaction
methotrexate: CB, drug combination
methotrexate: DT, drug therapy
methotrexate: IM, intramuscular drug administration
methotrexate: PO, oral drug administration
methotrexate: SC, subcutaneous drug administration
salazosulfapyridine: AE, adverse drug reaction
salazosulfapyridine: CB, drug combination
salazosulfapyridine: DT, drug therapy
hydroxychloroquine: AE, adverse drug reaction
hydroxychloroquine: CT, clinical trial
hydroxychloroquine: CB, drug combination
hydroxychloroquine: DT, drug therapy
cyclosporin: AE, adverse drug reaction
cyclosporin: CB, drug combination
cyclosporin: DT, drug therapy
gold: AE, adverse drug reaction
gold: CT, clinical trial
gold: CB, drug combination
gold: DT, drug therapy
gold: PO, oral drug administration
prednisone: AE, adverse drug reaction
prednisone: DT, drug therapy
prednisone: PO, oral drug administration
sulindac: DT, drug therapy
celecoxib: CT, clinical trial
celecoxib: DT, drug therapy
rofecoxib: DT, drug therapy
tenidap: DT, drug therapy
azathioprine: AE, adverse drug reaction
azathioprine: DT, drug therapy
cyclophosphamide: AE, adverse drug reaction
cyclophosphamide: DT, drug therapy
leflunomide: AE, adverse drug reaction
leflunomide: CT, clinical trial
leflunomide: DT, drug therapy
minocycline: AE, adverse drug reaction
minocycline: DT, drug therapy
penicillamine: AE, adverse drug reaction
penicillamine: DT, drug therapy
etanercept: AE, adverse drug reaction
etanercept: CT, clinical trial
etanercept: DT, drug therapy
etanercept: SC, subcutaneous drug administration
diclofenac: AE, adverse drug reaction
diclofenac: DT, drug therapy

etodolac: AE, adverse drug reaction
etodolac: DT, drug therapy
fenoprofen: AE, adverse drug reaction
fenoprofen: DT, drug therapy
ibuprofen: AE, adverse drug reaction
ibuprofen: DT, drug therapy
ketoprofen: AE, adverse drug reaction
ketoprofen: DT, drug therapy
nabumetone: AE, adverse drug reaction
nabumetone: DT, drug therapy
unindexed drug

RN (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (salazosulfapyridine) 599-79-1; (hydroxychloroquine) 118-42-3, 525-31-5; (**cyclosporin**) **79217-60-0**; (gold) 7440-57-5; (prednisone) 53-03-2; (sulindac) 38194-50-2; (celecoxib) 169590-42-5; (rofecoxib) **162011-90-7**, **186912-82-3**; (tenidap) 100599-27-7, **120210-48-2**; (azathioprine) 446-86-6; (cyclophosphamide) 50-18-0; (leflunomide) 75706-12-6; (minocycline) 10118-90-8, 11006-27-2, 13614-98-7; (penicillamine) 2219-30-9, 52-67-5; (etanercept) 185243-69-0, 200013-86-1; (diclofenac) 15307-79-6, 15307-86-5; (etodolac) 41340-25-4; (fenoprofen) 29679-58-1, 31879-05-7, 34691-31-1; (ibuprofen) 15687-27-1; (ketoprofen) 22071-15-4, 57495-14-4; (nabumetone) 42924-53-8

AB Rheumatoid arthritis (RA) is a systemic autoimmune disorder. Cartilage and bone destruction occur early in the disease. Although total remission is uncommon, therapy can slow the rate of disease progression. The majority of geriatric patients with RA developed the disease in mid-life, but some patients have elderly onset RA. Patients with elderly onset RA usually have a milder form of the disease than patients who develop RA earlier in life. Goals of therapy include controlling disease activity, slowing joint damage, decreasing pain and inflammation, and maintaining function for activities of daily living. Nonsteroidal anti-inflammatory drugs, corticosteroids, and disease modifying anti-rheumatic drugs (DMARDs) are the pharmacological agents most often used. DMARDs are now used earlier in the disease than in the past to control symptoms and to decrease joint destruction. The risks and benefits of therapy must be considered in developing a treatment plan for a geriatric patient. Geriatric patients are at increased risk for adverse effects from pharmacologic therapy compared to younger patients, and should be closely monitored for efficacy and toxicity.

L203 ANSWER 60 OF 70 EMBASE
on STN

ACCESSION NUMBER: 1998235212 EMBASE
TITLE: New prospects for the treatment of rheumatoid arthritis.
AUTHOR: Choy E.H.S.
CORPORATE SOURCE: E.H.S. Choy, Clinical/Academic Rheumatology Unit, King's College Hospital, East Dulwich Grove, London SE22 8PT, United Kingdom. e.choy@umds.ac.uk
SOURCE: Expert Opinion on Investigational Drugs, (1998) 7/7 (1087-1097).
Refs: 75
ISSN: 1354-3784 CODEN: EOIDER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 026 Immunology, Serology and Transplantation
030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

SUMMARY LANGUAGE: English
CT Medical Descriptors:
*rheumatoid arthritis: DT, drug therapy
*rheumatoid arthritis: EP, epidemiology
*rheumatoid arthritis: ET, etiology
synovitis: CO, complication
synovitis: DT, drug therapy
gastrointestinal toxicity: DT, drug therapy
gastrointestinal toxicity: PC, prevention
gastrointestinal toxicity: SI, side effect
immunomodulation
joint destruction: CO, complication
joint destruction: DT, drug therapy
joint destruction: PC, prevention
mortality
morbidity
osteoporosis: SI, side effect
human
review
Drug Descriptors:
*nonsteroid antiinflammatory agent: AE, adverse drug reaction
***nonsteroid antiinflammatory agent: CB, drug combination**
*nonsteroid antiinflammatory agent: CM, drug comparison
*nonsteroid antiinflammatory agent: DT, drug therapy
*nonsteroid antiinflammatory agent: PD, pharmacology
*corticosteroid: AE, adverse drug reaction
*corticosteroid: CM, drug comparison
*corticosteroid: DT, drug therapy
*corticosteroid: PD, pharmacology
*monoclonal antibody: AN, drug analysis
*monoclonal antibody: CM, drug comparison
*monoclonal antibody: DV, drug development
*monoclonal antibody: DT, drug therapy
*monoclonal antibody: PD, pharmacology
*antisense oligodeoxynucleotide: AN, drug analysis
*antisense oligodeoxynucleotide: CM, drug comparison
*antisense oligodeoxynucleotide: DV, drug development
*antisense oligodeoxynucleotide: PD, pharmacology
*cytokine: AN, drug analysis
*cytokine: CM, drug comparison
*cytokine: DV, drug development
*cytokine: PD, pharmacology
prostaglandin synthase: EC, endogenous compound
prostaglandin derivative: CB, drug combination
prostaglandin derivative: DT, drug therapy
proton pump inhibitor: CB, drug combination
proton pump inhibitor: DT, drug therapy
antihistaminic agent: CB, drug combination
antihistaminic agent: DT, drug therapy
cyclophosphamide: AE, adverse drug reaction
cyclophosphamide: CM, drug comparison
cyclophosphamide: DT, drug therapy
cyclophosphamide: PD, pharmacology
penicillamine: AE, adverse drug reaction
penicillamine: CB, drug combination
penicillamine: DT, drug therapy
penicillamine: PD, pharmacology
antimalarial agent: AE, adverse drug reaction
antimalarial agent: CM, drug comparison
antimalarial agent: DT, drug therapy

antimalarial agent: PD, pharmacology
gold derivative: AE, adverse drug reaction
gold derivative: CB, drug combination
gold derivative: CM, drug comparison
gold derivative: DT, drug therapy
gold derivative: PD, pharmacology
salazosulfapyridine: AE, adverse drug reaction
salazosulfapyridine: CB, drug combination
salazosulfapyridine: CM, drug comparison
salazosulfapyridine: DT, drug therapy
salazosulfapyridine: PD, pharmacology
cyclosporin: AE, adverse drug reaction
cyclosporin: CM, drug comparison
cyclosporin: DT, drug therapy
cyclosporin: PD, pharmacology
methotrexate: AE, adverse drug reaction
methotrexate: CB, drug combination
methotrexate: CM, drug comparison
methotrexate: DT, drug therapy
methotrexate: PD, pharmacology
deflazacort: AE, adverse drug reaction
deflazacort: CM, drug comparison
deflazacort: DT, drug therapy
deflazacort: PD, pharmacology
prednisolone: CM, drug comparison
prednisolone: DT, drug therapy
hydroxychloroquine: CB, drug combination
hydroxychloroquine: DT, drug therapy
azathioprine: CB, drug combination
azathioprine: DT, drug therapy
celebra: AN, drug analysis
celebra: CM, drug comparison
celebra: DV, drug development
celebra: PD, pharmacology
celecobix
cyclooxygenase 2 inhibitor: AN, drug analysis
cyclooxygenase 2 inhibitor: CM, drug comparison
cyclooxygenase 2 inhibitor: DV, drug development
cyclooxygenase 2 inhibitor: DT, drug therapy
cyclooxygenase 2 inhibitor: PD, pharmacology
tumor necrosis factor alpha antibody: AN, drug analysis
tumor necrosis factor alpha antibody: CM, drug comparison
tumor necrosis factor alpha antibody: DV, drug development
tumor necrosis factor alpha antibody: PD, pharmacology
bay 103356
tumor necrosis factor receptor fc fusion protein: AN, drug analysis
tumor necrosis factor receptor fc fusion protein: CM, drug comparison
tumor necrosis factor receptor fc fusion protein: DV, drug development
tumor necrosis factor receptor fc fusion protein: PD, pharmacology
tnfr 75 fc
lenercept: AN, drug analysis
lenercept: CM, drug comparison
lenercept: DV, drug development
lenercept: PD, pharmacology
recombinant interleukin 1 receptor blocking agent: AN, drug analysis
recombinant interleukin 1 receptor blocking agent: CM, drug comparison
recombinant interleukin 1 receptor blocking agent: DV, drug development
recombinant interleukin 1 receptor blocking agent: PD, pharmacology
unindexed drug
unclassified drug

RN (prostaglandin synthase) **39391-18-9**, **59763-19-8**, 9055-65-6; (cyclophosphamide) 50-18-0; (penicillamine) 2219-30-9, 52-67-5; (salazosulfapyridine) 599-79-1; (**cyclosporin**) **79217-60-0**; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (deflazacort) 14484-47-0; (prednisolone) 50-24-8; (hydroxychloroquine) 118-42-3, 525-31-5; (azathioprine) 446-86-6

AB Rheumatoid arthritis (RA) is a common inflammatory and destructive arthropathy. Current therapies fail to stop joint damage and reduce long-term disability. Greater understanding of disease pathogenesis has identified many inflammatory mediators as possible therapeutic targets. Novel therapeutic agents, such as monoclonal antibodies (mAbs), cytokine receptor-human immunoglobulin constructs, recombinant human proteins and antisense oligodeoxynucleotides targeting these inflammatory mediators have been tested in rheumatoid arthritis with some success. In particular, inflammation can be effectively suppressed using anticytokine therapies. However, the ideal treatment for RA, one that is immunomodulatory and induces prolonged disease remission after a single course of therapy, still eludes us. Strategies aiming to achieve this include TCR peptide vaccination and anti-CD4 mAbs, currently in clinical trials in RA.

L203 ANSWER 61 OF 70 EMBASE
on STN

ACCESSION NUMBER: 1998262990 EMBASE
TITLE: Current use of health status instruments in randomised controlled trials on patients with rheumatoid arthritis.
AUTHOR: Fransen J.; Stucki G.
CORPORATE SOURCE: G. Stucki, Rheumaklinik Inst Physikalishce Med, Universitatsspital, Gloriastrasse 25, CH-8091 Zurich, Switzerland. ruzstg@ruz.unizh.ch
SOURCE: Disease Management and Health Outcomes, (1998) 3/6 (271-277).
Refs: 32
ISSN: 1173-8790 CODEN: DMHOFV
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 031 Arthritis and Rheumatism
036 Health Policy, Economics and Management
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

CT Medical Descriptors:
*health status
*rheumatoid arthritis: DI, diagnosis
*rheumatoid arthritis: DT, drug therapy
*rheumatoid arthritis: TH, therapy
*outcomes research
questionnaire
treatment outcome
quality of life
medical assessment
symptomatology
patient counseling
training
relaxation training
muscle training
human
clinical trial
randomized controlled trial
review
Drug Descriptors:

diphtheria toxin interleukin 2: CT, clinical trial
diphtheria toxin interleukin 2: DT, drug therapy
tenidap: CT, clinical trial
tenidap: DT, drug therapy
antirheumatic agent: CT, clinical trial
antirheumatic agent: CM, drug comparison
antirheumatic agent: DT, drug therapy
meloxicam: CT, clinical trial
meloxicam: CM, drug comparison
meloxicam: DT, drug therapy
cd5 antigen: CT, clinical trial
cd5 antigen: DT, drug therapy
collagen type 2: CT, clinical trial
collagen type 2: DT, drug therapy
cyclosporin a: CT, clinical trial
cyclosporin a: CB, drug combination
cyclosporin a: CM, drug comparison
cyclosporin a: DT, drug therapy
pidotimod: CT, clinical trial
pidotimod: CB, drug combination
pidotimod: DT, drug therapy
penicillamine: CT, clinical trial
penicillamine: DT, drug therapy
methotrexate: CT, clinical trial
methotrexate: CM, drug comparison
methotrexate: DT, drug therapy
chloroquine: CT, clinical trial
chloroquine: CM, drug comparison
chloroquine: DT, drug therapy
naproxen: CT, clinical trial
naproxen: CM, drug comparison
naproxen: DT, drug therapy
aurothiomalate: CT, clinical trial
aurothiomalate: CM, drug comparison
aurothiomalate: DT, drug therapy
interleukin 1 receptor: CT, clinical trial
interleukin 1 receptor: DT, drug therapy

RN (tenidap) 100599-27-7, **120210-48-2**; (meloxicam) **71125-38-7**; (**cyclosporin** a) **59865-13-3**, **63798-73-2**; (pidotimod) 121808-62-6; (penicillamine) 2219-30-9, 52-67-5; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (chloroquine) 132-73-0, 3545-67-3, 50-63-5, 54-05-7; (naproxen) 22204-53-1, 26159-34-2; (aurothiomalate) 12244-57-4

AB This review examines the current use of health status instruments, such as questionnaires, in randomised clinical trials in rheumatoid arthritis (RA). A computer-assisted literature search was done using information from January 1996 until May 1997. The articles included were reviewed in a standardised way according to the kind of study-design, type of intervention, treatment arms, study population, follow-up, use of outcome measures, use of the core set and of the response criteria, and the results. 44 trials were identified and, of these, 31 were included. Of the 31 efficacy studies on RA patients, 10 did not use health status instruments. The most frequently used health status instruments were the Arthritis Impact Measurement Scales (AIMS) and the Stanford Health Assessment Questionnaire (HAQ). Of 21 studies, 5 showed a between-group difference with respect to health status. The main finding was that health status instruments are inconsistently used and lack full description and standardisation in their use as end-points in randomised clinical trials in RA.

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on STN
ACCESSION NUMBER: 97082040 EMBASE
DOCUMENT NUMBER: 1997082040
TITLE: Drug treatment of rheumatic diseases in the 1990s: Achievements and future developments.
AUTHOR: Choy E.H.S.; Scott D.L.
CORPORATE SOURCE: Dr. D.L. Scott, Clinical and Academic Rheumatology, King's College Hospital (Dulwich), East Dulwich Grove, London SE22 8PT, United Kingdom
SOURCE: Drugs, (1997) 53/3 (337-348).
Refs: 91
ISSN: 0012-6667 CODEN: DRUGAY
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Internal Medicine
030 Pharmacology
031 Arthritis and Rheumatism
033 Orthopedic Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
CT Medical Descriptors:
*arthritis: DT, drug therapy
*rheumatic disease: DT, drug therapy
alopecia: SI, side effect
antiinflammatory activity
article
biotechnology
bone atrophy: SI, side effect
cellular immunity
clinical trial
controlled study
drug selectivity
gastrointestinal symptom: SI, side effect
human
hypertension: SI, side effect
immunomodulation
major clinical study
meta analysis
nephrotoxicity: SI, side effect
osteoporosis: SI, side effect
rheumatoid arthritis: DT, drug therapy
synovitis: DT, drug therapy
t lymphocyte
vertigo: SI, side effect
Drug Descriptors:
*antiinflammatory agent: AE, adverse drug reaction
*antiinflammatory agent: CT, clinical trial
*antiinflammatory agent: DT, drug therapy
*antirheumatic agent: CT, clinical trial
*antirheumatic agent: DV, drug development
*antirheumatic agent: DT, drug therapy
antibiotic agent: CT, clinical trial
antibiotic agent: DT, drug therapy
cd4 antigen: EC, endogenous compound
corticosteroid: AE, adverse drug reaction
corticosteroid: CT, clinical trial
corticosteroid: AD, drug administration

corticosteroid: DO, drug dose
corticosteroid: DT, drug therapy
cyclooxygenase 2 inhibitor: PD, pharmacology
cyclosporin: CT, clinical trial
cyclosporin: AE, adverse drug reaction
cyclosporin: PR, pharmaceutics
cyclosporin: DT, drug therapy
cyclosporin: CB, drug combination
cyclosporin a: AE, adverse drug reaction
cyclosporin a: CT, clinical trial
cyclosporin a: DT, drug therapy
cyclosporin a: PR, pharmaceutics
cytokine: EC, endogenous compound
deflazacort: DT, drug therapy
deflazacort: CT, clinical trial
deflazacort: AE, adverse drug reaction
diclofenac: DT, drug therapy
diclofenac: CB, drug combination
immunoglobulin g: CT, clinical trial
immunoglobulin g: DO, drug dose
immunoglobulin g: DT, drug therapy
immunoglobulin g: PD, pharmacology
leflunomide: PD, pharmacology
leflunomide: DT, drug therapy
leflunomide: CT, clinical trial
leflunomide: AE, adverse drug reaction
meloxicam: PD, pharmacology
meloxicam: DT, drug therapy
meloxicam: CT, clinical trial
meloxicam: AE, adverse drug reaction
methotrexate: CT, clinical trial
methotrexate: CB, drug combination
methotrexate: DT, drug therapy
minocycline: DT, drug therapy
minocycline: CT, clinical trial
misoprostol: CB, drug combination
misoprostol: DT, drug therapy
monoclonal antibody: DV, drug development
monoclonal antibody: CT, clinical trial
nabumetone: CT, clinical trial
nabumetone: DT, drug therapy
nabumetone: AE, adverse drug reaction
nonsteroid antiinflammatory agent: DT, drug therapy
nonsteroid antiinflammatory agent: AE, adverse drug reaction
recombinant interleukin 1 receptor blocking agent: DV, drug development
rifampicin: CT, clinical trial
rifampicin: DT, drug therapy
tenidap: AE, adverse drug reaction
tenidap: CT, clinical trial
tenidap: DT, drug therapy
tenidap: PD, pharmacology
tumor necrosis factor antibody: DT, drug therapy
RN (**cyclosporin**) **79217-60-0**; (**cyclosporin** a) **59865-13-3**, **63798-73-2**; (deflazacort) 14484-47-0; (diclofenac) 15307-79-6, 15307-86-5; (immunoglobulin g) 97794-27-9; (leflunomide) 75706-12-6; (meloxicam) **71125-38-7**; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (minocycline) 10118-90-8, 11006-27-2, 13614-98-7; (misoprostol) 59122-46-2, 59122-48-4; (nabumetone) 42924-53-8; (rifampicin) 13292-46-1; (tenidap) 100599-27-7, **120210-48-2**; (tumor necrosis factor antibody) 162774-06-3

CN Neoral

AB There have been several advances in the therapy of arthritis. These are based on better understanding of the pathogenesis of rheumatic diseases, re-evaluation of previous therapeutic concepts such as combination therapy, and developments within biotechnology. There are 4 main areas of development, mainly involving the treatment of inflammatory synovitis. The first is with anti-inflammatory drugs, where there has been a focus on reducing gastrointestinal toxicity through the use of combination preparations such as diclofenac-misoprostol, and the introduction of drugs with more selectivity for cyclo-oxygenase-2 inhibition such as meloxicam. An additional approach has been the development of anti-inflammatory drugs such as tenidap which also control cytokine metabolism. The second area is slow-acting antirheumatic drugs with the introduction of **cyclosporin** as a single agent or in combination with methotrexate, the development of immunomodulating drugs such as leflunomide, and the demonstration that some antibiotics such as minocycline have slow-acting effects. The third area is the use of corticosteroids including the development of deflazacort as a bone sparing agent, the greater use of intramuscular depot steroids and the validation of low-dose oral corticosteroids in early rheumatoid arthritis. Finally, there have been advances in the biotechnology area with the demonstration that cytokine immunotherapy such as antibodies to tumour necrosis factor can rapidly improve the symptoms of rheumatoid arthritis, and that T cell immunotherapy with antibodies to the CD4 receptor may be effective in reducing synovitis. Many of these agents have not yet been introduced into clinical practice but they show the diversity of drug development and suggest the likelihood of major therapeutic benefits in the next few years.

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ACCESSION NUMBER: 95157766 EMBASE
DOCUMENT NUMBER: 1995157766
TITLE: New therapies for rheumatoid arthritis.
AUTHOR: Richardson C.; Emery P.
CORPORATE SOURCE: Rheumatology Rehab Research Unit, University of Leeds, 36 Clarendon Road,Leeds LS2 9NZ, United Kingdom
SOURCE: British Journal of Clinical Practice, (1995) 49/3 (135-139).
ISSN: 0007-0947 CODEN: BJCPAT
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

CT Medical Descriptors:
*rheumatoid arthritis: DT, drug therapy
drug efficacy
drug mixture
gastrointestinal symptom: DT, drug therapy
gastrointestinal symptom: PC, prevention
gastrointestinal symptom: SI, side effect
human
hypertension: SI, side effect
nephrotoxicity: SI, side effect
priority journal
proteinuria: SI, side effect

short survey
Drug Descriptors:
cd4 antigen: EC, endogenous compound
cyclosporin a: AE, adverse drug reaction
cyclosporin a: DT, drug therapy
diclofenac: CB, drug combination
diclofenac: DT, drug therapy
etodolac: DT, drug therapy
hr 325: DT, drug therapy
immunomodulating agent: AE, adverse drug reaction
immunomodulating agent: DT, drug therapy
interleukin 1 receptor blocking agent: DT, drug therapy
l 771726: DT, drug therapy
leflunomide: PK, pharmacokinetics
leflunomide: DT, drug therapy
meloxicam: DT, drug therapy
misoprostol: DT, drug therapy
misoprostol: CB, drug combination
monoclonal antibody: DT, drug therapy
nabumetone: PD, pharmacology
nabumetone: PK, pharmacokinetics
nabumetone: DT, drug therapy
nabumetone: AE, adverse drug reaction
naproxen: DT, drug therapy
naproxen: CB, drug combination
new drug: DT, drug therapy
new drug: DV, drug development
nonsteroid antiinflammatory agent: DT, drug therapy
nonsteroid antiinflammatory agent: CB, drug combination
nonsteroid antiinflammatory agent: AE, adverse drug reaction
prostaglandin synthase inhibitor: DT, drug therapy
tenidap: PD, pharmacology
tenidap: DT, drug therapy
tenidap: AE, adverse drug reaction
tumor necrosis factor alpha: EC, endogenous compound
unclassified drug

RN (**cyclosporin** a) **59865-13-3, 63798-73-2**; (diclofenac) 15307-79-6, 15307-86-5; (etodolac) 41340-25-4; (leflunomide) 75706-12-6; (meloxicam) **71125-38-7**; (misoprostol) 59122-46-2, 59122-48-4; (nabumetone) 42924-53-8; (naproxen) 22204-53-1, 26159-34-2; (tenidap) 100599-27-7, **120210-48-2**

CN L 771726; Hr 325

AB There are two major thrusts in the development of effective treatments in RA: the use and development of entirely new drugs; and the more effective usage of the currently available drugs. This represents a comprehensive review of the pharmacological agents that have been recently developed or will be available in the near future.

L203 ANSWER 64 OF 70 EMBASE
on STN

ACCESSION NUMBER: 95071438 EMBASE
DOCUMENT NUMBER: 1995071438
TITLE: Arachidonic acid may mediate the galanin-induced hyperpolarization in parasympathetic neurons from Necturus maculosus.
AUTHOR: Mulvaney J.M.; Parsons R.L.
CORPORATE SOURCE: Department of Anatomy/Neurobiology, University of Vermont, College of Medicine,Burlington, VT 05405, United States
SOURCE: Neuroscience Letters, (1995) 187/2 (95-98).
ISSN: 0304-3940 CODEN: NELED5

COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
CT Medical Descriptors:
*hyperpolarization
amphibia
animal tissue
article
controlled study
nonhuman
parasympathetic nerve
priority journal
Drug Descriptors:
*1 (5 isoquinolinesulfonyl) 2 methylpiperazine: CM, drug comparison
***4 bromophenacyl bromide: CB, drug combination**
*4 bromophenacyl bromide: CM, drug comparison
***4 bromophenacyl bromide: IT, drug interaction**
*4 bromophenacyl bromide: PD, pharmacology
*arachidonic acid: PD, pharmacology
*arachidonic acid: DO, drug dose
***arachidonic acid: CB, drug combination**
***arachidonic acid: IT, drug interaction**
***cyclosporin: CM, drug comparison**
*galanin: PD, pharmacology
***galanin: IT, drug interaction**
***galanin: CB, drug combination**
*phospholipase a2: EC, endogenous compound
*protein kinase inhibitor: CM, drug comparison
*protein kinase inhibitor: PD, pharmacology
***protein kinase inhibitor: CB, drug combination**
RN (1 (5 isoquinolinesulfonyl) 2 methylpiperazine) 84477-87-2; (4 bromophenacyl bromide) 99-73-0; (arachidonic acid) 506-32-1, 6610-25-9, 7771-44-0; (**cyclosporin**) **79217-60-0**; (galanin) 88813-36-9; (phospholipase a2) 9001-84-7
CN (1) H 7
CO (1) Rbi; Sigma; Sandoz (Switzerland)
AB The effects of **arachidonic** acid (AA) and compounds that **inhibit** intracellular signalling pathways on membrane potential and galanin-induced hyperpolarizations were investigated in parasympathetic neurons from Necturus maculosus. Treatment for 10-90 min with 10-20 μM 4-bromophenacylbromide or 10 μM **cyclosporin** A caused a progressive decrease in the amplitude of galanin-induced hyperpolarizations without any change in resting membrane potential. The galanin-induced hyperpolarization was not altered following a 10-120 min treatment with the protein kinase inhibitor H-7. These results indicated that phospholipase A2 activation, but not protein kinase activation, may be required for the galanin-induced hyperpolarization. Arachidonic acid (20-100 μM) caused a concentration-dependent membrane hyperpolarization of the parasympathetic neurons and a decrease in the amplitude of the galanin-induced hyperpolarization. These data indicate that phospholipase A2-catalyzed liberation of AA may be involved in the galanin-induced membrane hyperpolarization observed in mudpuppy parasympathetic neurons.

L203 ANSWER 65 OF 70 EMBASE
on STN
ACCESSION NUMBER: 94357321 EMBASE

DOCUMENT NUMBER: 1994357321
TITLE: Tepoxalin, a novel immunosuppressive agent with a different mechanism of action from **cyclosporin** A.
AUTHOR: Zhou L.; Ritchie D.; Wang E.Y.; Barbone A.G.; Argentieri D.; Lau C.Y.
CORPORATE SOURCE: Biologic Research, R. W. Johnson Pharmaceut. Res. Inst., 19 Green Belt Drive,Don Mills, Ont. M3C 1L9, Canada
SOURCE: Journal of Immunology, (1994) 153/11 (5026-5037).
ISSN: 0022-1767 CODEN: JOIMA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
CT Medical Descriptors:
*t lymphocyte
animal cell
article
controlled study
drug potency
drug potentiation
flow cytometry
gene
human
human cell
lymphocyte proliferation
mouse
nonhuman
polymerase chain reaction
priority journal
signal transduction
Drug Descriptors:
***cyclosporin a: CM, drug comparison**
***cyclosporin a: DO, drug dose**
***cyclosporin a: PD, pharmacology**
***cyclosporin a: IT, drug interaction**
***cyclosporin a: AD, drug administration**
*interleukin 2: EC, endogenous compound
*lipoxygenase: EC, endogenous compound
***lipoxygenase inhibitor: IT, drug interaction**
***lipoxygenase inhibitor: CM, drug comparison**
***lipoxygenase inhibitor: PD, pharmacology**
***propionamide derivative: IT, drug interaction**
*propionamide derivative: CM, drug comparison
*propionamide derivative: PD, pharmacology
*prostaglandin synthase: EC, endogenous compound
***prostaglandin synthase inhibitor: PD, pharmacology**
***prostaglandin synthase inhibitor: IT, drug interaction**
***prostaglandin synthase inhibitor: CM, drug comparison**
zileuton
aminophenol derivative
cd3 antigen: EC, endogenous compound
cd4 antigen: EC, endogenous compound
cd8 antigen: EC, endogenous compound
cytokine: EC, endogenous compound
dna: EC, endogenous compound
gamma interferon: EC, endogenous compound
immunosuppressive agent: CM, drug comparison

immunosuppressive agent: IT, drug interaction
immunosuppressive agent: PD, pharmacology
interleukin 2 receptor: EC, endogenous compound
ionomycin
leukotriene b4
messenger rna: EC, endogenous compound
naproxen
okt 3
phorbol 13 acetate 12 myristate
prostaglandin e2
recombinant interleukin 2
tepoxalin: CM, drug comparison
tepoxalin: IT, drug interaction
tepoxalin: PD, pharmacology

RN (**cyclosporin** a) **59865-13-3**, **63798-73-2**; (interleukin 2) 85898-30-2; (lipoxygenase) 9027-17-2, 9029-60-1; (prostaglandin synthase) **39391-18-9**, **59763-19-8**, 9055-65-6; (zileuton) **111406-87-2**, 132880-11-6; (dna) 9007-49-2; (gamma interferon) 82115-62-6; (ionomycin) 56092-81-0; (leukotriene b4) 71160-24-2; (naproxen) 22204-53-1, 26159-34-2; (okt 3) 140608-64-6; (phorbol 13 acetate 12 myristate) 16561-29-8; (prostaglandin e2) 363-24-6; (**recombinant** interleukin 2) 110942-02-4; (tepoxalin) **103475-41-8**

CN (1) Sandimmune

CO (1) Sandoz (Canada); R w johnson pharmaceutical research institute (United States)

AB Tepoxalin, a compound previously identified as a **dual cyclooxygenase/lipoxygenase** (CO/LO) **inhibitor**, is a potent inhibitor of T cell proliferation. Comparing the suppressive effects of tepoxalin and **cyclosporin** A (CsA) on OKT3-, PMA-, IL-2-, and PMA + ionomycin-induced T cell proliferations revealed marked differences in the mechanism of action between the two compounds. Whereas CsA was most effective in suppressing OKT3- stimulated proliferation, tepoxalin was more potent in inhibiting PMA-, PMA + ionomycin-, and IL-2-induced proliferation. Quantitative PCR (QPCR) assays used to detect cytokine messages showed that tepoxalin blocked IL-2 mRNA transcription in PMA- and PMA + ionomycin-, but not OKT3-stimulated T cells whereas CsA was most potent in inhibiting OKT3-induced IL-2 mRNA induction in these cells. Both tepoxalin and CsA did not inhibit the expression of IL-2R; however, only tepoxalin, but not CsA, inhibited the proliferation of IL-2-dependent blasts and the transcription of IFN-γ, an IL-2-dependent target gene. Moreover, addition of exogenous IL-2 restored OKT3-induced proliferation to CsA- but not tepoxalin-treated cells. These data suggest that tepoxalin, but not CsA, suppressed T cell proliferation by inhibiting IL-2-induced signal transduction. Consistent with these findings, tepoxalin, unlike CsA, which was most potent when added at the initiation of OKT3 stimulation, was equally active, regardless of whether it was added at the beginning or 48 h after culture initiation. The difference in mechanism of action between tepoxalin and CsA was confirmed further by the **synergistic** suppressive effects on T cell proliferation upon co-administration of the two compounds.

L203 ANSWER 66 OF 70 EMBASE on STN

ACCESSION NUMBER: 93280287 EMBASE
DOCUMENT NUMBER: 1993280287
TITLE: Lysophospholipid-mediated inhibition of Na+,K+-adenosine triphosphatase is a possible mechanism of immunosuppressive activity of **cyclosporin** A.
AUTHOR: Anderson R.; Smit M.J.; Van Rensburg C.E.J.

CORPORATE SOURCE: Institute for Pathology, P.O. Box 2034,Pretoria 0001, South Africa
SOURCE: Molecular Pharmacology, (1993) 44/3 (605-614).
ISSN: 0026-895X CODEN: MOPMA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
CT Medical Descriptors:
*enzyme inhibition
*immunosuppressive treatment
article
controlled study
dose response
drug mechanism
enzyme activity
human
human cell
lymphocyte activation
lymphocyte proliferation
nephrotoxicity
priority journal
t lymphocyte
Drug Descriptors:
*adenosine triphosphatase (potassium sodium): EC, endogenous compound
***cyclosporin a: CB, drug combination**
***cyclosporin a: DO, drug dose**
***cyclosporin a: PD, pharmacology**
*lysophospholipid
1 (5 isoquinolinesulfonyl) 2 methylpiperazine: PD, pharmacology
alpha tocopherol: CB, drug combination
alpha tocopherol: PD, pharmacology
arachidonic acid
butylated hydroxyanisole: PD, pharmacology
butylated hydroxyanisole: CB, drug combination
butylcresol: PD, pharmacology
butylcresol: CB, drug combination
catalase
cysteine
indometacin: PD, pharmacology
lipoxygenase inhibitor: PD, pharmacology
lysophosphatidylcholine
lysophospholipase: EC, endogenous compound
nordihydroguaiaretic acid: PD, pharmacology
phytohemagglutinin
piroxicam: PD, pharmacology
potassium ion
prostaglandin e2
prostaglandin synthase
protein kinase c
retinol: PD, pharmacology
staurosporine: PD, pharmacology
thymidine
RN (**cyclosporin** a) **59865-13-3, 63798-73-2**; (1 (5 isoquinolinesulfonyl) 2 methylpiperazine) 84477-87-2; (alpha tocopherol) 1406-18-4, 1406-70-8, 52225-20-4, 58-95-7, 59-02-9; (arachidonic acid) 506-32-1, 6610-25-9, 7771-44-0; (butylated

hydroxyanisole) 25013-16-5; (butylcresol) 128-37-0, 30587-81-6; (catalase) 9001-05-2; (cysteine) 4371-52-2, 52-89-1, 52-90-4; (indometacin) 53-86-1, 74252-25-8, 7681-54-1; (lysophosphatidylcholine) 93794-93-5; (lysophospholipase) 9001-85-8; (nordihydroguaiaretic acid) 500-38-9; (phytohemagglutinin) 9008-97-3; (piroxicam) 36322-90-4; (potassium ion) 24203-36-9; (prostaglandin e2) 363-24-6; (prostaglandin synthase) **39391-18-9**, **59763-19-8**, 9055-65-6; (protein kinase c) 141436-78-4; (retinol) 68-26-8, 82445-97-4; (staurosporine) 62996-74-1; (thymidine) 50-89-5

CO Sandoz (Switzerland); Sigma (United States); Hoffmann la roche (Switzerland); Pfizer (South Africa)

AB The relationship between the phospholipase-stimulating and immunosuppressive properties of **cyclosporin** A (CsA) has been investigated in vitro. At concentrations of 0.025 μM and upwards, CsA caused dose-related inhibition of both mitogen- and alloantigen-stimulated uptake of tritiated thymidine by human mononuclear leukocytes (MNL), which was associated with a time- and dose-related enhancement of the generation of lysophosphatidylcholine (LPC), arachidonic acid, and prostaglandin E2 from mitogen-stimulated cells. Arachidonate alone, at concentrations of up to 20 μM, did not affect lymphocyte activation, whereas **cyclooxygenase** and **5'- lipoxygenase inhibitors** failed to protect the cells against the antiproliferative effects of CsA. However, LPC caused dose-related inhibition of MNL proliferation. Moreover, coincubation of MNL with α-tocopherol, a lysophospholipid-complexing agent, or with lysophospholipase protected the cells against CsA, as well as against LPC. The Na+,K+-ATPase activity of mitogen-activated lymphocytes was also inhibited by CsA, whereas inclusion of α-tocopherol or lysophospholipase protected this enzyme. Excessive production of lysophospholipids and consequent inhibition of Na+,K+-ATPase during CsA treatment of mitogen- or antigen-activated lymphocytes is a possible biochemical mechanism of the immunosuppressive activity of this agent.

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ACCESSION NUMBER: 92218798 EMBASE
DOCUMENT NUMBER: 1992218798
TITLE: Possible mechanism of immunosuppressive effect of scoparone (6,7-dimethoxycoumarin).
AUTHOR: Huang H.-C.; Huang Y.-L.; Chang J.-H.; Chen C.-C.; Lee Y.-T.
CORPORATE SOURCE: Department of Pharmacology, College of Medicine, National Taiwan University, No. 1, Jen-Ai Road,Taipei, Taiwan,Province of China
SOURCE: European Journal of Pharmacology, (1992) 217/2-3 (143-148). ISSN: 0014-2999 CODEN: EJPHAZ
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

CT Medical Descriptors:
*arachidonic acid metabolism
*lymphocyte proliferation
***mixed lymphocyte reaction**
*mononuclear cell

article
concentration response
controlled study
enzyme immunoassay
gene expression
human
human cell
normal human
priority journal
Drug Descriptors:
interleukin 2 receptor
***cyclosporin: PD, pharmacology**
***cyclosporin: CM, drug comparison**
*genistein: PD, pharmacology
*genistein: CM, drug comparison
*immunosuppressive agent: CM, drug comparison
*immunosuppressive agent: PD, pharmacology
*interleukin 1: EC, endogenous compound
*interleukin 2: EC, endogenous compound
*scoparone: CM, drug comparison
*scoparone: PD, pharmacology
2,3 dinorthromboxane b2: EC, endogenous compound
alloxan: TO, drug toxicity
enzyme inhibitor: PD, pharmacology
enzyme inhibitor: CM, drug comparison
indometacin: PD, pharmacology
leukotriene b4: EC, endogenous compound
mepacrine: PD, pharmacology
nordihydroguaiaretic acid: PD, pharmacology
phytohemagglutinin: PD, pharmacology
prostaglandin e2: EC, endogenous compound
prostaglandin f2 alpha: EC, endogenous compound
protein tyrosine kinase: EC, endogenous compound
thromboxane derivative: EC, endogenous compound

RN (**cyclosporin**) **79217-60-0**; (genistein) 446-72-0; (interleukin 2) 85898-30-2; (scoparone) 120-08-1; (2,3 dinorthromboxane b2) 63250-09-9; (alloxan) 3237-50-1, 50-71-5; (indometacin) 53-86-1, 74252-25-8, 7681-54-1; (leukotriene b4) 71160-24-2; (mepacrine) 69-05-6, 83-89-6; (nordihydroguaiaretic acid) 500-38-9; (phytohemagglutinin) 9008-97-3; (prostaglandin e2) 363-24-6; (prostaglandin f2 alpha) 551-11-1; (protein tyrosine kinase) 80449-02-1

CO Aldrich (United States); Gibco (United States); Sigma (United States); Sandoz (Switzerland); Biomol research laboratories (United States)

AB The possible mechanism of the immunosuppressive effect of scoparone (6,7-dimethoxycoumarin) was investigated. Human peripheral blood mononuclear cells (106 cells/ml) were stimulated with 0.25% phytohemagglutinin (PHA) and the proliferative response was determined from the uptake of tritiated thymidine. Scoparone (10-6 to 3 x 10-4 M) reduced the proliferative response in a dose-dependent manner. The proliferative response of mononuclear cells to **mixed** lymphocyte reaction was also reduced by scoparone (10-5 to 10-4 M). Interleukin-1, interleukin-2 production and interleukin-2 receptor expression were all reduced in the presence of scoparone. Scoparone (10 and 30 μM) significantly reduced the suppression elicited by the diabetogenic drug, alloxan (10 mM). The suppressive activity of scoparone was significantly reduced by quinacrine (a phospholipase A2 **inhibitor**), indomethacin (a **cyclooxygenase inhibitor**) and nordihydroguaiaretic acid (a **lipoxygenase inhibitor**). The levels of prostaglandin E2, prostaglandin F(2α), leukotriene B4 and 2,3-dinor-thromboxane B2 in culture medium of PHA-stimulated

mononuclear cells, measured with an enzyme immunoassay, were elevated by scoparone treatment. We compared the effect of scoparone on the mononuclear cell response to genistein, a specific inhibitor of protein tyrosine kinase and demonstrated the non-additivity and cross-desensitization of the two compounds. Our results suggest that the immunosuppressive effect of scoparone may be exerted in part through inhibition of protein tyrosine kinase and release of arachidonic acid metabolites.

L203 ANSWER 68 OF 70 EMBASE
on STN

ACCESSION NUMBER: 89203323 EMBASE
DOCUMENT NUMBER: 1989203323
TITLE: **Interaction** of **cyclosporine**-A with the renin-angiotensin system in canine veins.
AUTHOR: Muler-Schweinitzer E.
CORPORATE SOURCE: Preclinical Research, Sandoz Ltd., CH-4002 Basle, Switzerland
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology, (1989) 340/2 (252-257).
ISSN: 0028-1298 CODEN: NSAPCC
COUNTRY: Germany
DOCUMENT TYPE: Journal
FILE SEGMENT: 002 Physiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
CT Medical Descriptors:
*renin angiotensin aldosterone system
*saphenous vein
dog
drug concentration
vasoconstriction
vasodilatation
animal experiment
animal cell
nonhuman
intravenous drug administration
oral drug administration
priority journal
Drug Descriptors:
***cyclosporin a: PD, pharmacology**
angiotensin
angiotensin i
bradykinin
clopramin
dazoxiben
enalaprilat
h 77
indometacin
kallikrein
noradrenalin
nordihydroguaiaretic acid
papaverine
prostaglandin f2 alpha
unclassified drug
RN (**cyclosporin** a) **59865-13-3, 63798-73-2**;
(angiotensin) 11128-99-7, 1407-47-2; (angiotensin i) 9041-90-1;
(bradykinin) 58-82-2, 5979-11-3; (dazoxiben) 74226-22-5, 78218-09-4;

(enalaprilat) 76420-72-9; (h 77) 82131-82-6, 82167-03-1; (indometacin) 53-86-1, 74252-25-8, 7681-54-1; (kallikrein) 8006-48-2, 9001-01-8; (noradrenalin) 1407-84-7, 51-41-2; (nordihydroguaiaretic acid) 500-38-9; (papaverine) 58-74-2, 61-25-6; (prostaglandin f2 alpha) 551-11-1

CN (1) H 77; (2) Hypertensin; (3) Paveron; (4) Sandimmune

CO (1) Bachem (Switzerland); (2) Ciba geigy (Switzerland); (3) Karlspharma (Germany); (4) Sandoz (Switzerland); Hoechst (Germany); Sigma (Germany); Merck sharp and dohme (United States); Pfizer (United Kingdom)

AB Responses of canine saphenous veins to bradykinin and angiotensin and the effect of **cyclosporine**-A were investigated both in conscious dogs in vivo and on ring preparations from canine saphenous veins in vitro. In vivo local infusion of bradykinin into the saphenous vein elicited dose-dependent reduction in compliance, i.e., venoconstriction, whereas local infusion of angiotensin elicited dose-dependent venodilation, which was markedly enhanced during blockade of endogenous thromboxane A2 synthesis by dazoxiben (2.5 mg/kg i.v.). The venocostrictor response to bradykinin was attenuated after oral administration of both the thiazide-like diuretic clopamide (0.5 mg/kg) or **cyclosporine** -A (30 mg/kg), and by concomitant local infusion of **cyclosporine** -A (1-10 μg/min). Systemic i.v. infusion of the renin inhibitor H-77 (0.1 mg/kg/h) reversed the inhibition of bradykinin by both clopamide and **cyclosporine**-A. In vitro bradykinin elicited relaxation at low (0.1-10 nmol/l) but constriction at higher concentrations. The venoconstrictor response to bradykinin was resistant to blockade of thromboxane A2 synthesis and only partially attenuated after selective **blockade** of **cyclooxygenase** or **lipoxygenase.** Concomitant **blockade** of both **lipoxygenase** and **cyclooxygenase** activity by nordihydroguaiaretic acid (NDGA 10-30 μmol/l) nearly abolished the contractile response thereby enhancing the relaxant component of the bradykinin effect. Angiotensin II also elicited biphasic responses of partially contracted venous rings. Concomitant **blockade** of both **lipoxygenase** and **cyclooxygenase** by NDGA (10 μol/l) again attenuated the contractile component of the angiotensin effect thereby unmasking the venodilator activity which could be inhibited by the angiotensin II receptor blocker saralasin (0.01 -1 μmol/l). Blockade of converting enzyme by enalaprilic acid, the active metabolite of the converting enzyme inhibitor enalapril, attenuated responses to angiotensin I but shifted the concentration-response curve to bradykinin to the left. Compared to angiotensin I or angiotensin II, angiotensinogen was about ten times less potent in relaxing venous rings, but its potency was enhanced by a factor 10 in the presence of the serine protease kallikrein. Neither in the absence nor in the presence of kallikrein did the renin inhibitor H-77 modify the venodilator responses to angiotensinogen in vitro. Furthermore, venous responses to both bradykinin and angiotensinogen were unchanged in rings incubated for 1 h with 1 μmol/l **cyclosporine**-A. It is suggested, that the venoconstrictor response to bradykinin is mediated through enhanced formation and/or release of both prostaglandins and leukotrienes and that the bradykinin effect is modulated by endogenous angiotensin. Furthermore, the present data suggest (1) that the canine saphenous vein possesses a local renin-angiotensin system with activatable angiotensin forming enzyme(s) and (2) that activation of circulating prorenin rather than of tissue renin contributes to the vascular effect of **cyclosporine** -A.

L203 ANSWER 69 OF 70 EMBASE on STN

ACCESSION NUMBER: 87050286 EMBASE

DOCUMENT NUMBER: 1987050286

TITLE: Prolactin-dependent mitogenesis in Nb 2 node lymphoma

cells: Effects of immunosuppressive cyclopeptides.
AUTHOR: Russell D.H.; Buckley A.R.; Montgomery D.W.; et al.
CORPORATE SOURCE: Department of Pharmacology, University of Arizona College of Medicine, Tucson, AZ 85724, United States
SOURCE: Journal of Immunology, (1987) 138/1 (276-284).
CODEN: JOIMA3
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
003 Endocrinology
026 Immunology, Serology and Transplantation
025 Hematology
016 Cancer
LANGUAGE: English
CT Medical Descriptors:
*drug efficacy
***drug interaction**
*drug receptor binding
*lymphoma cell
mitogenesis
rat
tumor cell culture
priority journal
drug administration
methodology
nonhuman
lymphatic system
in vitro study
Drug Descriptors:
***cyclosporin**
***cyclosporin a**
*didemnin b
*ornithine decarboxylase
*prolactin
*prolactin receptor
*protein kinase c
calcimycin
indometacin
phorbol ester
radioisotope
RN (**cyclosporin**) **79217-60-0**; (**cyclosporin** a) **59865-13-3**, **63798-73-2**; (didemnin b) 77327-05-0; (ornithine decarboxylase) 9024-60-6; (prolactin) 12585-34-1, 50647-00-2, 9002-62-4; (protein kinase c) 141436-78-4; (calcimycin) 52665-69-7; (indometacin) 53-86-1, 74252-25-8, 7681-54-1
CO Sandoz (Switzerland); Sigma (United States)
AB Prolactin (PRL)-stimulated ornithine decarboxylase (ODC) activity and subsequent proliferation are inhibited by the cyclopeptides **cyclosporine** (CsA) and didemnin B (DB) in Nb 2 node lymphoma cells. Similar concentrations of these agents also inhibit 125I-PRL binding, suggesting that their inhibitory effects on these PRL-dependent physiologic responses are mediated at least in part at the level of PRL receptor **interactions.** The phorbol ester TPA stimulated ODC activity and [3H]thymidine incorporation to 54% and 31% that of a near-optimal mitogenic concentration of PRL (10 ng/ml), suggesting that mitogenesis in these cells is coupled to some degree to the activation of protein kinase C (PKC). The calcium ionophore A23187 increased ODC activity only slightly and actually decreased [3H]thymidine incorporation to a value below the 'cells only' controls. The addition of TPA plus

A23187 did not further enhance the effects of TPA to elevate ODC activity and [3H]thymidine incorporation. However, A23187 significantly elevated PRL-stimulated ODC activity with a subsequent inhibition of [3H]thymidine incorporation, suggesting a block of entry into S phase. Both cyclopeptides decreased the elevation of ODC activity in G1 phase of cell cycle in response to PRL, suggestive of a site of action for these agents in early G1, a conclusion compatible with their ability to inhibit PRL binding to these cells. Addition of CsA or CB2 hr after PRL had no effect on PRL-stimulated ODC activity detectable at 6 hr, but addition of either as late as 6 hr still affected the extent of mitogenesis. This is in line with the requirement for PRL to be present in the culture medium for a minimum of 3 to 6 hr to invoke a maximal effect on mitogenesis. Addition of either cyclopeptide after the cells were in S phase had no effect on the extent of [3H]thymidine incorporation. An **inhibitor** of the **cyclooxygenase** pathway (indomethacin) enhanced both PRL-stimulated ODC activity and proliferation, whereas **inhibition** of the **lipoxygenase** pathway by NDGA attenuated only proliferation, suggesting that in Nb 2 cells, products of the lipoxygenase pathway may contribute to the mechanism of PRL-stimulated mitogenesis. Because Nb 2 lymphoma cells were derived from estrogenized rats, estrogen was tested as a mitogen. By itself it was not mitogenic, but in conjunction with PRL, estradiol-17β elevated the ODC response and inhibited proliferation. Inhibitors of PKC known to have minimal effects on RNA synthesis, quercetin and gossypol, totally inhibited both the elevations of ODC activity and [3H]thymidine incorporation in response to PRL in Nb 2 lymphoma cells. Quinacrine, an inhibitor of phospholipase A2 and C activities, also inhibited PRL-stimulated ODC activity and mitogenesis. These data suggest that a common physiologic site of action of the cyclopeptides CsA and DB in Nb 2 lymphoma cells is the alteration of PRL receptor-mediated activity, and further substantiate a role for PKC in the coupling of PRL receptors to the stimulation of ODC activity and mitogenesis in Nb 2 lymphoma cells.

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ACCESSION NUMBER: 86089045 EMBASE
DOCUMENT NUMBER: 1986089045
TITLE: Modulation of mouse ear edema by **cyclooxygenase** and **lipoxygenase inhibitors** and other pharmacologic agents.
AUTHOR: Carlson R.P.; O'Neill-Davis L.; Chang J.; Lewis A.J.
CORPORATE SOURCE: Department of Experimental Therapeutics, Wyeth Laboratories, Inc., Philadelphia, PA 19101, United States
SOURCE: Agents and Actions, (1985) 17/2 (197-204).
CODEN: AGACBH
COUNTRY: Switzerland
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
LANGUAGE: English
CT Medical Descriptors:
*capillary permeability
*diphenyl disulfide
*edema
animal model
ear
mouse
auditory system
peripheral vascular system
oral drug administration

nonhuman
animal experiment
Drug Descriptors:
*tomelukast
*phenidone
*2 aminomethyl 4 tert butyl 6 iodophenol
*[2 cyano 3 (methylamino)anilino]oxoacetic acid
*[[3 [3 (4 acetyl 3 hydroxy 2 propylphenoxy) 2 hydroxypropoxy] 2 cyanophenyl]amino]oxoacetic acid ethyl ester
*acetylsalicylic acid
*alpha pentyl 3 (2 quinolylmethoxy)benzyl alcohol
*antiinflammatory agent
*arachidonic acid
*atropine
*auranofin
*benoxaprofen
*betamethasone
*3 amino 1 (3 trifluoromethylphenyl) 2 pyrazoline
*chloroquine
*chlorpheniramine
*chlorpromazine
*cimetidine
***prostaglandin synthase inhibitor**
*cyclophosphamide
***cyclosporin a**
*dapsone
*dazoxiben
*desipramine
*dexamethasone
*diazepam
*etretinate
*fentiazac
*forskolin
*glyceryl trinitrate
*haloperidol
*hydrochlorothiazide
*ibuprofen
*indometacin
*isosorbide dinitrate
*isotretinoin
*levamisole
***lipoxygenase inhibitor**
*methylprednisolone
*methysergide
*nafazatrom
*phorbol 13 acetate 12 myristate
*piroxicam
*promethazine
*timegadine
*tolmetin
*zomepirac
6 anilino 5,8 quinolinequinone

RN (tomelukast) 88107-10-2; (phenidone) 92-43-3; (2 aminomethyl 4 tert butyl 6 iodophenol) 58456-91-0; ([2 cyano 3 (methylamino)anilino]oxoacetic acid) 63365-44-6; ([[3 [3 (4 acetyl 3 hydroxy 2 propylphenoxy) 2 hydroxypropoxy] 2 cyanophenyl]amino]oxoacetic acid ethyl ester) 91327-53-6; (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (alpha pentyl 3 (2 quinolylmethoxy)benzyl alcohol) **101910-24-1**; (arachidonic acid) 506-32-1, 6610-25-9, 7771-44-0; (atropine) 51-55-8, 55-48-1; (auranofin) 34031-32-8; (benoxaprofen)

51234-28-7; (betamethasone) 378-44-9; (3 amino 1 (3 trifluoromethylphenyl) 2 pyrazoline) 66000-40-6; (chloroquine) 132-73-0, 3545-67-3, 50-63-5, 54-05-7; (chlorpheniramine) 132-22-9; (chlorpromazine) 50-53-3, 69-09-0; (cimetidine) 51481-61-9, 70059-30-2; (cyclophosphamide) 50-18-0; (**cyclosporin** a) **59865-13-3, 63798-73-2**; (dapsone) 80-08-0; (dazoxiben) 74226-22-5, 78218-09-4; (desipramine) 50-47-5, 58-28-6; (dexamethasone) 50-02-2; (diazepam) 439-14-5; (etretinate) 54350-48-0; (fentiazac) 18046-21-4; (forskolin) 66575-29-9; (glyceryl trinitrate) 55-63-0; (haloperidol) 52-86-8; (hydrochlorothiazide) 58-93-5; (ibuprofen) 15687-27-1; (indometacin) 53-86-1, 74252-25-8, 7681-54-1; (isosorbide dinitrate) 87-33-2; (isotretinoin) 4759-48-2; (levamisole) 14769-73-4, 16595-80-5; (methylprednisolone) 6923-42-8, 83-43-2; (methysergide) 16509-15-2, 361-37-5, 62288-72-6; (nafazatrom) 59040-30-1; (phorbol 13 acetate 12 myristate) 16561-29-8; (piroxicam) 36322-90-4; (promethazine) 58-33-3, 60-87-7; (timegadine) 71079-19-1; (tolmetin) 26171-23-3, 35711-34-3; (zomepirac) 33369-31-2, 64092-48-4; (6 anilino 5,8 quinolinequinone) 91300-60-6

CN Aspirin; Bw 775 c; Mk 447; Wy 44329; Ly 83583; Ly 171883; Rev 5901 a; Wy 41195

CO Nu chek; Sk & f; Merck; Richardson merrell; Mcneil; Upjohn; Leo; Sigma; Lilly; Aldrich; Pfizer; Merck sharp and dohme; Sandoz; Knoll; Whitehall; Mead johnson; Wyeth; Ives; Miles; Ayerst

AB **Inhibitors** of **arachidonic** acid (AA) metabolism and other pharmacologic agents were evaluated against ear edema produced in mice by tetradecanoylphorbol acetate (TPA) or AA. Drugs were administered orally and topically either 30 min prior to AA or 30 min after TPA, except for steroids which were administered 2.5-3 hr prior to AA. Several **cyclooxygenase** (CO) **inhibitors** including indomethacin, aspirin, piroxicam and timegadine were without effect when administered orally against either irritant; the same drugs inhibited TPA edema when they were administered topically. **Mixed** CO/**lipoxygenase** (LO) **inhibitors**, phenidone and BW755C, were active orally against AA edema (ED50s of 84 and 65 mg/kg, respectively) and against TPA edema (ED50s of 235 and 88 mg/kg, respectively). Phenidone was more active topically against AA edema (ED50, 0.1 mg/ear) than BW755C (ED50, 2.8 mg/ear); however, BW755C was more active topically against TPA edema (ED50, 0.2 mg/ear) than phenidone (ED50, 0.6 mg/ear). Methylprednisolone was very effective in the AA (oral ED50, 17 mg/kg; topical ED50, > 1 mg/ear) and TPA models (oral ED50, 4.3 mg/kg; topical ED50, 0.03 mg/ear. MK-447 was topically and orally effective only in the TPA model. Not surprisingly, drugs were more effective topically than orally in both mouse ear edema assays. The models were somewhat selective for CO and CO/LO inhibitors; however, dapsone was orally effective in the ear models, and a number of mediator antagonists and CNS drug, especially anti-psychotics were topically active primarily against TPA edema. These models may be useful for the detection of in vivo activity of CO/LO or 5-LO inhibitors.

=>

=> fil zcaplus

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FILE COVERS 1907 - 30 Jul 2004 VOL 141 ISS 6
FILE LAST UPDATED: 29 Jul 2004 (20040729/ED)

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FILE LAST UPDATED: 29 Jul 2004 (20040729/ED)

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=> fil biosis

FILE 'BIOSIS' ENTERED AT 12:18:56 ON 30 JUL 2004

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 29 July 2004 (20040729/ED)

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FILE RELOADED: 19 October 2003.

=> FIL HOME

FILE 'HOME' ENTERED AT 12:19:01 ON 30 JUL 2004

=> d que l174
L164          364 SEA FILE=HCAPLUS ABB=ON  PLU=ON  GREGORY, S?/AU
L165          148 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ISAKSON, P?/AU
L166         2490 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANDERSON, G?/AU
L167         2960 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L164 OR L165 OR L166)
L168           91 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L167 AND ?CYCLOOXYGENASE?
L169           10 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L168 AND ?LIPOXYGENASE?
L173           76 SEA FILE=HCAPLUS ABB=ON  PLU=ON  FENNESSY,M?/AU
L174            8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L169 NOT L173


=>

=> d que l181
L175          658 SEA FILE=BIOSIS ABB=ON  PLU=ON  GREGORY, S?/AU
L176          188 SEA FILE=BIOSIS ABB=ON  PLU=ON  ISAKSON, P?/AU
L177         3136 SEA FILE=BIOSIS ABB=ON  PLU=ON  ANDERSON, G?/AU
L178         3938 SEA FILE=BIOSIS ABB=ON  PLU=ON  (L175 OR L176 OR L177)
L179          113 SEA FILE=BIOSIS ABB=ON  PLU=ON  L178 AND (?CYCLOOXYGENAS? OR
                  COX)
L180           21 SEA FILE=BIOSIS ABB=ON  PLU=ON  L179 AND (?LIPOXYGENAS? OR
                  ?ARACHIDON?)
L181           18 SEA FILE=BIOSIS ABB=ON  PLU=ON  L180 AND ?INHIBIT?


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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jul 23, 2004 (20040723/UP).

=> dup rem l174 l181

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FILE 'BIOSIS' ENTERED AT 12:20:05 ON 30 JUL 2004
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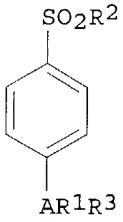
PROCESSING COMPLETED FOR L181
L204           23 DUP REM L174 L181 (3 DUPLICATES REMOVED)
                  ANSWERS '1-8' FROM FILE HCAPLUS
                  ANSWERS '9-23' FROM FILE BIOSIS

=> d ibib abs 1-
YOU HAVE REQUESTED DATA FROM 23 ANSWERS - CONTINUE? Y/(N):y
```

L204 ANSWER 1 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2000:754502 HCAPLUS
DOCUMENT NUMBER: 133:321880
TITLE: Treatment of inflammation and inflammation-related disorders with a combination of a **cyclooxygenase**-2 inhibitor and a 5-**lipoxygenase** inhibitor.
INVENTOR(S): **Isakson, Peter C.; Anderson, Gary D.; Gregory, Susan A.**
PATENT ASSIGNEE(S): G.D. Searle and Co., USA
SOURCE: U.S., 21 pp., Cont.-in-part of U.S. Ser. No. 489,472, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6136839	A	20001024	US 1996-661660	19960611
CA 2224517	AA	19961227	CA 1996-2224517	19960611

PRIORITY APPLN. INFO.: US 1995-489472 B2 19950612
OTHER SOURCE(S): MARPAT 133:321880
GI



I

AB A combination comprising a 5-**lipoxygenase** inhibitor and a **cyclooxygenase**-2 inhibitor selected from title compds. [I; A = pyrazolyl; R1 = ≥1 of (substituted) heterocyclyl, cycloalkyl, cycloalkenyl, aryl; R2 = Me, amino; R3 = H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, CO2H, cyanoalkyl, heterocyclyloxy, alkoxy, alkylthio, alkylcarbonyl, aryl, haloalkyl, etc.], is claimed. Thus, EtO2CCHF2 in MeOCMe3 was treated with NaOMe and then with 3-fluoro-4-methoxyacetophenone (preparation given) followed by 16 h stirring to give 96% 4,4-difluoro-1-(3-fluoro-4-methoxyphenyl)butane-1,3-dione. This was refluxed 16 h with 4-sulfonamidophenylhydrazine hydrochloride in EtOH to give 87% 4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl-1H-pyrazol-1-yl]benzenesulfonamide (II). II with 6-[[3-fluoro-5-(3,4,5,6-tetrahydro-4-methoxy-2H-pyran-4-yl)phenoxy]methyl]-1-methyl-1H-quinazolin-2-one (III) at 30 mpk/day orally in mice in the collagen-induced arthritis screen reduced incidence of arthritis to 20% (vs. 100% for controls). A formulation containing II and III is given.
REFERENCE COUNT: 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L204 ANSWER 2 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 1994:455773 HCAPLUS
DOCUMENT NUMBER: 121:55773

TITLE: In vivo characterization of zymosan-induced mouse peritoneal inflammation
AUTHOR(S): Rao, Tadimeti S.; Currie, Jerry L.; Shaffer, Alex F.; **Isakson, Peter C.**
CORPORATE SOURCE: Inflammatory Dis. Res., Searle Res. Dev., St. Louis, MO, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1994), 269(3), 917-25
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

AB I.p. administration of zymosan to mice resulted in marked biosynthesis of eicosanoids and influx of neutrophils with distinct time course profiles. 6-Keto-prostaglandin-F1α (6-KPA) increased between 30 and 60 min and rapidly decreased thereafter. Leukotriene (LT)C4 levels showed similar patterns, but were sustained for several hours. LTB4 increased in a biphasic manner with peak increases between 2 to 3 h. Repeated injections with zymosan suggested that incoming neutrophils generate most of the LTB4. Myeloperoxidase (MPO), an enzyme marker for neutrophils, continued to increase throughout the time course. Mast cells regulate LTB4 biosynthesis and neutrophil trafficking, whereas resident macrophages contribute to 6-KPA and LTC4 biosynthesis. The complement fragment C5a has a minimal role in zymosan-induced inflammation. Selective 5-**lipoxygenase** (5-LO) inhibitors, zileuton {N(1-benzo[b]thienyl-2yl-ethyl)-N-hydroxyurea}, TZI-41127 {2-(4-hydroxy-3,5-dimethylphenyl)-5-methoxy-3-methylindole} and **cyclooxygenase** (CO) inhibitors selectively modulated eicosanoid biosynthesis. Both 5-LO and CO inhibitors attenuated influx of neutrophils to varying degrees. A LTB4 receptor antagonist, SC-41930 {7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)-propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid} and an LTD4 receptor antagonist, LY-171883 {1-(2-hydroxy-3-propyl-4-(4-1H-tetrazol-5-yl)butoxy-phenylethanone)} (i.v.) attenuated influx of neutrophils and associated LTB4 biosynthesis. These results suggest that both 5-LO and CO metabolites regulate neutrophil influx in this model. Marked eicosanoid biosynthesis and cellular influx in response to zymosan provides an attractive exptl. paradigm to evaluate anti-inflammatory effects of inhibitors of arachidonate CO or 5-LO pathways.

L204 ANSWER 3 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 1995:132001 HCAPLUS
DOCUMENT NUMBER: 122:560
TITLE: Phorbol ester-induced dermal inflammation in mice: evaluation of inhibitors of 5-**lipoxygenase** and antagonists of leukotriene B4 receptor
AUTHOR(S): Rao, Tadimeti S.; Yu, Stella S.; Djuric, Stevan W.; **Isakson, Peter C.**
CORPORATE SOURCE: Inflammatory Dis. Res., St. Louis, MO, 63198, USA
SOURCE: Journal of Lipid Mediators and Cell Signalling (1994), 10(3), 213-28
CODEN: JLMSEO; ISSN: 0929-7855
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the present investigation, the effects of selective inhibitors of 5-**lipoxygenase** (5-LO), zileuton and TZI-41127, E-6080, AA-861 and antagonists of leukotriene B4 (LTB4) receptors, SC-41930, and SC-51146 and a selective **cyclooxygenase** inhibitor, indomethacin, were examined in TPA-induced acute mouse dermal inflammation. Topical application of all these agents, except indomethacin, resulted in marked attenuation of TPA-induced edema and influx of neutrophils reflected in myeloperoxidase measurements. Topically applied SC-41930 attenuated TPA-induced edema and

neutrophil influx in a dose-related manner. Oral administration of LTB4 receptor antagonists either as a pre-treatment or post-treatment attenuated TPA-induced edema and influx of neutrophils. The O-demethyl analog of SC-41930, SC-37920, which was nearly 1000-fold less active than SC-41930 in LTB4 receptor binding assays, was inactive in inflammation assays, suggesting a role for LTB4 in this response. Zileuton and TZI-41127 were more effective as anti-inflammatory agents following oral administration that after i.p. administration. I.p. administered indomethacin attenuated edema response but not influx of neutrophils. Taken together, these results suggest a role for leukotrienes in acute inflammation induced by TPA and possible utility of this model to test in vivo 5-LO inhibitors and LTB4 receptor antagonists.

L204 ANSWER 4 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:562996 HCAPLUS
DOCUMENT NUMBER: 127:239123
TITLE: Combinations having immunosuppressive effects, containing **cyclooxygenase**-2-inhibitors and 5-**lipoxygenase** inhibitors
INVENTOR(S): **Gregory, Susan A.; Isakson, Peter C. ; Anderson, Gary**
PATENT ASSIGNEE(S): G.D. Searle and Co., USA; Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9729776	A1	19970821	WO 1997-US1558	19970212
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2246265	AA	19970821	CA 1997-2246265	19970212
AU 9718505	A1	19970902	AU 1997-18505	19970212
EP 888127	A1	19990107	EP 1997-904133	19970212
EP 888127	B1	20011212		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2000504723	T2	20000418	JP 1997-529363	19970212
AT 210461	E	20011215	AT 1997-904133	19970212
PT 888127	T	20020531	PT 1997-904133	19970212
ES 2169351	T3	20020701	ES 1997-904133	19970212
US 6376528	B1	20020423	US 1999-430072	19991018
US 2002143033	A1	20021003	US 2002-98644	20020315

PRIORITY APPLN. INFO.: US 1996-600622 A1 19960213
WO 1997-US1558 W 19970212
US 1998-189463 B1 19981110
US 1999-430072 A3 19991018

OTHER SOURCE(S): MARPAT 127:239123

AB Treatment with a **cyclooxygenase**-2 inhibitor and a 5-**lipoxygenase** inhibitor is described as being useful in reducing recipient rejection of transplanted organs and for treatment of autoimmune

diseases. 4-[5-(3-Fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide and N'-[3-[5-(4-fluorophenoxy)-2-furyl]-1-methyl-2-propynyl]-N'-hydroxyurea were prepared and a combination of these 2 compds. showed a delay in rejection time of skin grafts while treatment alone of each of these compds. resulted in no prolongation of graft survival.

L204 ANSWER 5 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:161901 HCAPLUS
TITLE: New dual inhibitors of inducible **cyclooxygenase** (COX-2) and leukotriene biosynthesis as potential new therapeutic agents for rheumatoid arthritis
AUTHOR(S): Sikorski, James A.; Talley, John J.; Norman, Bryan H.; Graneto, Matthew J.; Lu, Hwang-Fun; Devadas, Balekudru; Brown, David L.; **Anderson, Gary D.** ; Veenhuizen, Amy W.; et al.
CORPORATE SOURCE: G. D. Searle RandD, St. Louis, MO, 63198, USA
SOURCE: Book of Abstracts, 213th ACS National Meeting, San Francisco, April 13-17 (1997), MEDI-069. American Chemical Society: Washington, D. C.
CODEN: 64AOAA
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Pro-inflammatory products of arachidonic acid metabolism mediated by either the prostaglandin or leukotriene pathways have been implicated in many models of inflammatory disease. Consequently, compds. that inhibit the production of both prostaglandins and leukotrienes may exhibit beneficial anti-inflammatory properties. The recent discovery of an inducible **cyclooxygenase** (COX-2) has led to potent and selective COX-2 inhibitors with GI-sparing, anti-inflammatory activity. These results suggest that dual inhibitors of COX-2 and either 5-**lipoxygenase** (5-LO) or LTA4 hydrolase (LTA4H) could be even more effective anti-inflammatory agents. A medicinal chemical strategy will be presented which combines either a 5-LO or LTA4H pharmacophore with a selective, oxazole-based COX-2 inhibitor. Single mols. establishing a chemical proof of concept will be presented that inhibit either the COX-2 and 5-LO or COX-2 and LTA4H enzymes.

L204 ANSWER 6 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:174992 HCAPLUS
DOCUMENT NUMBER: 126:166479
TITLE: Compositions comprising a **cyclooxygenase**-2 inhibitor and a 5-**lipoxygenase** inhibitor for treatment of inflammation and inflammation-related disorders
INVENTOR(S): **Isakson, Peter C.**; **Anderson, Gary D.** ; **Gregory, Susan A.**
PATENT ASSIGNEE(S): G.D. Searle and Co., USA
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9641626	A1	19961227	WO 1996-US10106	19960611

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS,

LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN

CA 2224517	AA	19961227	CA 1996-2224517	19960611
AU 9661117	A1	19970109	AU 1996-61117	19960611
EP 833622	A1	19980408	EP 1996-918465	19960611
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 11507670	T2	19990706	JP 1997-503273	19960611

PRIORITY APPLN. INFO.: US 1995-489472 A 19950612
WO 1996-US10106 W 19960611

OTHER SOURCE(S): MARPAT 126:166479

AB Combinations of a **cyclooxygenase**-2 inhibitor and a 5-**lipoxygenase** inhibitor are described for treatment of inflammation and inflammation-related disorders. Preparation of e.g. 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is described., as are pharmaceutical formulations and activity against collagen-induced arthritis in mice.

L204 ANSWER 7 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:182220 HCAPLUS
DOCUMENT NUMBER: 120:182220
TITLE: Calcium ionophore (A-23187)-induced peritoneal eicosanoid biosynthesis: A rapid method to evaluate inhibitors of arachidonic acid metabolism in vivo
AUTHOR(S): Rao, T. S.; Currie, J. L.; Shaffer, A. F.; **Isakson, P. C.**
CORPORATE SOURCE: Monsanto Co., St Louis, MO, 63198, USA
SOURCE: Mediators of Inflammation (1993), 2(5), 357-62
CODEN: MNFLEF; ISSN: 0962-9351
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present investigation characterizes calcium ionophore (A-23187)-induced peritoneal eicosanoid biosynthesis in the rat. I.p. injection of A-23187 (20 μg/rat) stimulated marked biosynthesis of 6-keto-PGF1α (6-KPA), TxB2, LTC4 and LTB4, with no detectable changes on levels of PGE2. Levels of all eicosanoids decreased rapidly after a peak which was seen as early as 5 min. Enzyme markers of cellular contents of neutrophils and mononuclear cells, MPO and NAG resp., decreased rapidly after ionophore injection; this was followed by increases after 60 min. Indomethacin, a selective **cyclooxygenase** inhibitor, and zileuton and ICI D-2138, two selective 5-**lipoxygenase** inhibitors attenuated prostaglandin and leukotriene pathways resp. Oral administration of zileuton (20 mg/kg, p.o.) inhibited LTB4 biosynthesis for up to 6 h suggesting a long duration of pharmacol. activity in the rats consistent with its longer half-life. The rapid onset and the magnitude of increases in levels of eicosanoids render the ionophore-induced peritoneal eicosanoid biosynthesis a useful model to evaluate pharmacol. profiles of inhibitors of eicosanoid pathways in vivo.

L204 ANSWER 8 OF 23 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:69016 HCAPLUS
DOCUMENT NUMBER: 120:69016
TITLE: Evaluation of 5-**lipoxygenase** inhibitors, zileuton, A-78773 and ICI-D-2138 in an ionophore (A-23187)-induced pleural inflammation model in the rat
AUTHOR(S): Rao, Tadimeti S.; Currie, Jerry L.; Shaffer, Alexander F.; **Isakson, Peter C.**
CORPORATE SOURCE: Monsanto Co., St. Louis, MO, 63198, USA

SOURCE: Life Sciences (1993), 53(9), PL147-PL152
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Intrapleural injection of A-23187 (10 μg), a calcium ionophore, elicited rapid increase in biosynthesis of prostaglandins and leukotrienes in a time-dependent manner. 6-Keto-prostaglandin-F1α (6-KPA) was the principal **cyclooxygenase** product with modest increases in levels of thromboxane B2 and prostaglandin-E2. Orally administered indomethacin, a selective **cyclooxygenase** inhibitor, and three selective 5-**lipoxygenase** inhibitors, zileuton, A-78773 and ICI-D-2138 markedly attenuated arachidonate pathways with projected ED50 values of < 1-2 mg/kg. Furthermore, a single oral administration of either ICI-D-2138 or A-78773 (each 20 mg/kg, po) resulted in persistent inhibition of 5-**lipoxygenase** pathway for up to 24 h. These results indicate zileuton, A-78773 and ICI-D-2138 to be potent and selective inhibitors of 5-LO and document the utility of A-23187-induced pleural inflammation in evaluating efficacy of inhibitors of arachidonic acid metabolism in vivo.

L204 ANSWER 9 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:314309 BIOSIS
DOCUMENT NUMBER: PREV200200314309
TITLE: Immunosuppressive effects of administration of a **cyclooxygenase**-2 **inhibitor** and a 5-**lipoxygenase inhibitor.**
AUTHOR(S): **Gregory, Susan A** [Inventor, Reprint author]; **Isakson, Peter C** [Inventor]; **Anderson, Gary** [Inventor]
CORPORATE SOURCE: St. Louis, MO, USA
ASSIGNEE: G. D. Searle and Co.
PATENT INFORMATION: US 6376528 April 23, 2002
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Apr. 23, 2002) Vol. 1257, No. 4. http://www.uspto.gov/web/menu/patdata.html. e-file.
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 29 May 2002
Last Updated on STN: 29 May 2002
AB A method to suppress immune, acute or delayed-type hypersensitivity by treatment with a combination of a therapeutically-effective amount of a 5-**lipoxygenase inhibitor** and a **cyclooxygenase**-2 **inhibitor** is reported. The method may be used, for example, to suppress the immune response associated with organ transplantation, graft versus host disease, and conditions with underlying autoimmune or inflammatory reactivities or responses.

L204 ANSWER 10 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:509444 BIOSIS
DOCUMENT NUMBER: PREV200100509444
TITLE: Neuronal expression of **cyclooxygenase** 2 increases stroke damage.
AUTHOR(S): Dore, S. [Reprint author]; Sugo, N. [Reprint author]; **Isakson, P.**; Worley, P.; Traystman, R. J. [Reprint author]; Koehler, R. C. [Reprint author]; Hurn, P. D. [Reprint author]; Andreasson, K.
CORPORATE SOURCE: Dept Anesth/Critical Care Med., Johns Hopkins Univ Sch Med, Baltimore, MD, USA
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1,

pp. 878. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001.
ISSN: 0190-5295.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Oct 2001
Last Updated on STN: 23 Feb 2002

AB The **cyclooxygenases** (**COX**) catalyze the conversion of **arachidonic** acid to thromboxanes and prostaglandins. Our previous studies of genes involved in the adaptive responses of neurons to synaptic activity, we demonstrated **COX**-2 as a NMDA-dependent activity-regulated gene in the brain. There are two isoforms of **cyclooxygenase**: **COX**-1 is expressed constitutively in most tissues and is present in normal conditions at very low levels in the brain; **COX**-2 is highly expressed in neurons of hippocampus, amygdala and layers II/III of cortex in paradigms of excitotoxicity, such as kindling, traumatic head injury and in stroke. As a model of increased neuronal **COX** activity, we have generated lines of transgenic mice that overexpress the human isoform of **COX**-2 (hCOX-2) under the control of a neuronal promotor. We observed higher **COX**-2 levels in the hippocampus, cortex and striatum and we quantified in brain homogenates an overproduction of prostaglandins close to 6 fold. After submitting these mice to transient cerebral ischemia by performing middle cerebral artery occlusion (MCAO) (1 hour) and then allowing reperfusion (4 days), we observed increase infarction volume in mice overexpressing **COX**-2 (45.7+6.4 mm3, mean+SEM, n=10) as compared to non-transgenic littermates (25.2+4.0 mm3, n=17) ($p<0.05$). These findings demonstrate that increased neuronal **COX** activity is detrimental to excitotoxic-induced injury. Limiting **COX**-2 enzymatic activity with specific **inhibitors** may be a potential strategy to protect against neuronal injury induced by cerebral ischemia.

L204 ANSWER 11 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:100696 BIOSIS
DOCUMENT NUMBER: PREV200000100696
TITLE: Effects of celecoxib, a novel **cyclooxygenase**-2 **inhibitor**, on platelet function in healthy adults: A randomized, controlled trial.
AUTHOR(S): Leese, Philip T.; Hubbard, Richard C.; Karim, Aziz; **Isakson, Peter C.**; Yu, Shawn S.; Geis, G. Steven [Reprint author]
CORPORATE SOURCE: Searle Clinical Research, 4901 Searle Parkway, A3E, Skokie, IL, 60077, USA
SOURCE: Journal of Clinical Pharmacology, (Feb., 2000) Vol. 40, No. 2, pp. 124-132. print.
CODEN: JCPCBR. ISSN: 0091-2700.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Mar 2000
Last Updated on STN: 3 Jan 2002

AB Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) nonspecifically **inhibit cyclooxygenase**-1 (**COX**-1), an enzyme critical to normal platelet function, and **COX**-2, which mediates inflammatory response mechanisms. Celecoxib, an antiarthritic agent that **inhibits COX**-2 but spares **COX**-1 at therapeutic doses, is expected to have minimal effects on platelet function. A double-blind, randomized, placebo-controlled study of 10 days' duration

was conducted in 24 healthy adults to compare the effects on platelet function of a supratherapeutic dose of celecoxib (600 mg bid) with a standard dose of naproxen (500 mg bid), a conventional NSAID. Ex vivo platelet aggregation in response to standard agonists (collagen, **arachidonate**, or U46619 (a thromboxane A2 receptor agonist)), bleeding time, and serum thromboxane B2 (TxB2) level were measured. Unlike celecoxib or placebo, naproxen produced statistically significant reductions in platelet aggregation and serum TxB2 levels and increased bleeding time. The results indicate that even at supratherapeutic doses, celecoxib will not interfere with normal mechanisms of platelet aggregation and hemostasis, supporting the premise that celecoxib is **COX**-1 sparing relative to conventional NSAIDs.

L204 ANSWER 12 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:896 BIOSIS
DOCUMENT NUMBER: PREV199900000896
TITLE: Pharmacological analysis of **cyclooxygenase**-1 in inflammation.
AUTHOR(S): Smith, Christopher J.; Zhang, Yan; Koboldt, Carol M.; Muhammad, Jerry; Zweifel, Ben S.; Shafer, Alex; Talley, John J.; Masferrer, Jaime L.; Seibert, Karen; **Isakson, Peter C.** [Reprint author]
CORPORATE SOURCE: Searle Res. Development, 700 Chesterfield Parkway North, St. Louis, MO 63198, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (Oct. 27, 1998) Vol. 95, No. 22, pp. 13313-13318. print.
CODEN: PNASA6. ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Jan 1999
Last Updated on STN: 11 Jan 1999

AB The enzymes **cyclooxygenase**-1 and **cyclooxygenase**-2 (**COX**-1 and **COX**-2) catalyze the conversion of **arachidonic** acid to prostaglandin (PG) H2, the precursor of PGs and thromboxane. These lipid mediators play important roles in inflammation and pain and in normal physiological functions. While there are abundant data indicating that the inducible isoform, **COX**-2, is important in inflammation and pain, the constitutively expressed isoform, **COX**-1, has also been suggested to play a role in inflammatory processes. To address the latter question pharmacologically, we used a highly selective **COX**-1 **inhibitor**, SC-560 (**COX**-1 IC50 = 0.009 muM; **COX**-2 IC50 = 6.3 muM). SC-560 **inhibited COX**-1-derived platelet thromboxane B2, gastric PGE2, and dermal PGE2 production, indicating that it was orally active, but did not **inhibit COX**-2-derived PGs in the lipopolysaccharide-induced rat air pouch. Therapeutic or prophylactic administration of SC-560 in the rat carrageenan footpad model did not affect acute inflammation or hyperalgesia at doses that markedly **inhibited** in vivo **COX**-1 activity. By contrast, celecoxib, a selective **COX**-2 **inhibitor**, was anti-inflammatory and analgesic in this model. Paradoxically, both SC-560 and celecoxib reduced paw PGs to equivalent levels. Increased levels of PGs were found in the cerebrospinal fluid after carrageenan injection and were markedly reduced by celecoxib, but were not affected by SC-560. These results suggest that, in addition to the role of peripherally produced PGs, there is a critical, centrally mediated neurological component to inflammatory pain that is mediated at least in part by **COX**-2.

L204 ANSWER 13 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1998:163956 BIOSIS
DOCUMENT NUMBER: PREV199800163956
TITLE: Regulation of prostaglandin biosynthesis in vivo by glutathione.
AUTHOR(S): Margalit, Alon; Hauser, Scott D.; Zweifel, Ben S.; Anderson, Melissa A.; **Isakson, Peter C.** [Reprint author]
CORPORATE SOURCE: Searle Res. Dev., 700 Chesterfield Parkway N., St. Louis, MO 63198, USA
SOURCE: American Journal of Physiology, (Feb., 1998) Vol. 274, No. 2 PART 2, pp. R294-R302. print.
CODEN: AJPHAP. ISSN: 0002-9513.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Apr 1998
Last Updated on STN: 6 Apr 1998

AB Intraperitoneal administration of urate crystals to mice reduced subsequent macrophage conversion of **arachidonic** acid (AA) to prostaglandins (PGs) and 12-hydroxyeicosatetraenoic acid for up to 6 h. In contrast, levels of 12-hydroxyheptadecatrienoic acid (12-HHT) were markedly elevated. This metabolic profile was previously observed in vitro when recombinant **cyclooxygenase** (**COX**) enzymes were incubated with reduced glutathione (GSH). Analysis of peritoneal GSH levels revealed a fivefold elevation after urate crystal administration. The GSH synthesis **inhibitor** L-buthionine-(S,R)-sulfoximine partially reversed the urate crystal effect on both GSH elevation and PG synthesis. Moreover, addition of exogenous GSH to isolated peritoneal macrophages shifted AA metabolism from PGs to 12-HHT. Urate crystal administration reduced **COX**-1, but induced **COX**-2 expression in peritoneal cells. The reduction of **COX**-1 may contribute to the attenuation of PG synthesis after 1 and 2 h, but PG synthesis remained **inhibited** up to 6 h, when **COX**-2 levels were high. Overall, our results indicate that elevated GSH levels **inhibit** PG production in this model and provide in vivo evidence for the role of GSH in the regulation of PG biosynthesis.

L204 ANSWER 14 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1997:261255 BIOSIS
DOCUMENT NUMBER: PREV199799567858
TITLE: **Inhibition** of human colon cancer cell growth by selective **inhibition** of **cyclooxygenase** -2.
AUTHOR(S): Sheng, Hongmiao; Shao, Jinyi; Kirkland, Susan C.; **Isakson, Peter**; Coffey, Robert J.; Morrow, Jason; Beauchamp, R. Daniel; Dubois, Raymond N.
CORPORATE SOURCE: Dep. Med./GI, MCN C-2104, Vanderbilt Univ. Med. Cent., Nashville, TN 37232-2279, USA
SOURCE: Journal of Clinical Investigation, (1997) Vol. 99, No. 9, pp. 2254-2259.
CODEN: JCINAO. ISSN: 0021-9738.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Jun 1997
Last Updated on STN: 24 Jun 1997

AB A considerable amount of evidence collected from several different experimental systems indicates that **cyclooxygenase**-2 (**COX**-2) may play a role in colorectal tumorigenesis. Large epidemiologic studies have shown a 40-50% reduction in mortality from colorectal cancer in persons taking aspirin or other nonsteroidal

antiinflammatory drugs on a regular basis. One property shared by all of these drugs is their ability to **inhibit COX**, a key enzyme in the conversion of **arachidonic** acid to prostaglandins. Two isoforms of **COX** have been characterized, **COX**-1 and **COX**-2. **COX**-2 is expressed at high levels in intestinal tumors in humans and rodents. In this study, we selected two transformed human colon cancer cell lines for studies on the role of **COX**-2 in intestinal tumorigenesis. We evaluated HCA-7 cells which express high levels of **COX**-2 protein constitutively and HCT-116 cells which lack **COX**-2 protein. Treatment of nude mice implanted with HCA-7 cells with a selective **COX**-2 **inhibitor** (SC-58125), reduced tumor formation by 85-90%. SC-58125 also **inhibited** colony formation of cultured HCA-7 cells. Conversely, SC-58125 had no effect on HCT-116 implants in nude mice or colony formation in culture. Here we provide evidence that there may be a direct link between **inhibition** of intestinal cancer growth and selective **inhibition** of the **COX**-2 pathway.

L204 ANSWER 15 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1997:197743 BIOSIS
DOCUMENT NUMBER: PREV199799496946
TITLE: New dual **inhibitors** of inducible **cyclooxygenase** (COS-2) and leukotriene biosynthesis as potential new therapeutic agents for rheumatoid arthritis.
AUTHOR(S): Sikorski, James A.; Talley, John J.; Noman, Bryan H.; Graneto, Matthew J.; Lu, Hwang-Fun; Devadas, Balekudru; Brown, David L.; **Anderson, Gray D.**; Veenhuizen, Amy W.; McGarity, Kelly L.; Askonas, Leslie J.; Koboldt, Carol M.; Keith, Robert H.; **Gregory, Susan A.**
CORPORATE SOURCE: G.D. Searle R and D, 700 Chesterfield Parkway North, St. Louis, MO 63198, USA
SOURCE: Abstracts of Papers American Chemical Society, (1997) Vol. 213, No. 1-3, pp. MEDI 69.
Meeting Info.: 213th National Meeting of the American Chemical Society. San Francisco, California, USA. April 13-17, 1997.
CODEN: ACSRAL. ISSN: 0065-7727.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 May 1997
Last Updated on STN: 2 Jun 1997

L204 ANSWER 16 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1997:41491 BIOSIS
DOCUMENT NUMBER: PREV199799333479
TITLE: Structural basis for selective **inhibition** of cyclooxyenase-2 by anti-inflammatory agents.
AUTHOR(S): Kurumbail, Ravi G. [Reprint author]; Stevens, Anna M.; Gierse, James K.; McDonald, Joseph J.; Stegeman, Roderick A.; Pak, Jina Y.; Gildehaus, Daniel; Miyashiro, Julie M.; Penning, Thomas D.; Seibert, Karen; **Isakson, Peter C.**; Stallings, William C.
CORPORATE SOURCE: G.D. Searle, 700 Chesterfield Parkway North, St. Louis, MO 63198, USA
SOURCE: Nature (London), (1996) Vol. 384, No. 6610, pp. 644-648.
CODEN: NATUAS. ISSN: 0028-0836.
DOCUMENT TYPE: Article
LANGUAGE: English

ENTRY DATE: Entered STN: 28 Jan 1997
Last Updated on STN: 28 Jan 1997

AB Prostaglandins and glucocorticoids are potent mediators of inflammation. Non-steroidal anti-inflammatory drugs (NSAIDs) exert their effects by **inhibition** of prostaglandin production. The pharmacological target of NSAIDs is **cyclooxygenase** (**COX**, also known as PHG synthase), which catalyses the first committed step in **arachidonic**-acid metabolism. Two isoforms of the membrane protein **COX** are known: **COX**-1, which is constitutively expressed in most tissues, is responsible for the physiological production of prostaglandins,; and **COX**-2, which is induced by cytokines, mitogens and endotoxins in inflammatory cells, is responsible for the elevated production of prostaglandins during inflammation. The structure of ovine **COX**-1 complexed with several NSAIDs has been determined. Here we report the structures of unliganded murine **COX**-2 and complexes with flurbiprofen, indomethacin and SC-558, a selective **COX**-2 **inhibitor**, determined at 3.0 to 2.5 ANG resolution. These structures explain the structural basis for the selective **inhibition** of **COX**-2, and demonstrate some of the conformational changes associated with time-dependent **inhibition.**

L204 ANSWER 17 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1995:124837 BIOSIS
DOCUMENT NUMBER: PREV199598139137
TITLE: Expression and selective **inhibition** of the constitutive and inducible forms of human cyclo-oxygenase.
AUTHOR(S): Gierse, James K.; Hauser, Scott D.; Creely, David P.; Koboldt, Carol; Rangwala, Shaukat H.; **Isakson, Peter C.**; Seibert, Karen [Reprint author]
CORPORATE SOURCE: Searle Inflammatory Disease Res., Monsanto Company, 800 N. Lindberg Boulevard, St. Louis MO 63167, USA
SOURCE: Biochemical Journal, (1995) Vol. 305, No. 2, pp. 479-484. ISSN: 0264-6021.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Mar 1995
Last Updated on STN: 29 Mar 1995

AB The enzyme cyclo-oxygenase catalyses the oxygenation of **arachidonic** acid, leading to the formation of prostaglandins. Recently two forms of cyclo-oxygenase have been described: a constitutive (**COX**-1) enzyme present in most cells and tissues, and an inducible (**COX**-2) isoenzyme observed in many cells in response to pro-inflammatory cytokines. Constitutive and inducible forms of human cyclo-oxygenase (hCOX-1 and hCOX2) were cloned and expressed in insect cells, utilizing a baculovirus expression system. hCOX-1 had a specific activity of 18.8 mu-mol of O-2/mg with a K-m of 13.8 mu-M for **arachidonate** and V-maximum of 1500 nmol of O-2/nmol of enzyme, whereas hCOX-2 had a specific activity of 12.2 mu-mol of O-2/mg with a K-m of 8.7 mu-M for **arachidonate** and a V-maximum of 1090 nmol of O-2/nmol of enzyme. Indomethacin **inhibited** both hCOX-1 and hCOX-2, whereas NS-398 and Dup-697 selectively **inhibited** hCOX-2. Both NS-398 and Dup-697 exhibited time-dependent inactivation of hCOX-2, as did indomethacin on both enzymes. The competitive **inhibitor** of hCOX-1, mefenamic acid, also displayed competitive **inhibition** of hCOX-2. These results demonstrate the ability to generate selective non-steroidal anti-inflammatory drugs (NSAIDs), which could provide useful improvement therapeutically in the treatment of chronic inflammatory disease.

L204 ANSWER 18 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1995:83000 BIOSIS
DOCUMENT NUMBER: PREV199598097300
TITLE: Pharmacological and biochemical demonstration of the role of **cyclooxygenase** 2 in inflammation and pain.
AUTHOR(S): Seibert, Karen [Reprint author]; Zhang, Yan; Leahy, Kathleen; Hauser, Scott; Masferrer, Jaime; Perkins, William; Lee, Len; **Isakson, Peter**
CORPORATE SOURCE: G.D. Searle, Monsanto Co., 800 North Lindbergh Boulevard, St. Louis, MO 63167, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1994) Vol. 91, No. 25, pp. 12013-12017.
CODEN: PNASA6. ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Feb 1995
Last Updated on STN: 27 Apr 1995

AB Nonsteroidal antiinflammatory drugs (NSAIDs) are widely used for the treatment of inflammatory diseases, but significant side effects such as gastrointestinal erosion and renal damage limit their use. NSAIDs **inhibit** the enzyme **cyclooxygenase** (**COX**), which catalyzes the conversion of **arachidonic** acid to prostaglandins (PGs) and thromboxane. Two forms of **COX** have been identified--**COX**-1, which is constitutively expressed in most tissues and organs, and the inducible enzyme, **COX**-2, which has been localized primarily to inflammatory cells and tissues. In an animal model of acute inflammation (injection of carrageenan into the footpad), edema was produced that was associated with marked accumulation of **COX**-2 mRNA and thromboxane. A selective **inhibitor** of **COX**-2 (SC-58125) **inhibited** edema at the inflammatory site and was analgesic but had no effect on PG production in the stomach and did not cause gastric toxicity. These data suggest that selective **inhibition** of **COX**-2 may produce superior antiinflammatory drugs with substantial safety advantages over existing NSAIDs.

L204 ANSWER 19 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1995:68463 BIOSIS
DOCUMENT NUMBER: PREV199598082763
TITLE: Beta-Adrenoceptors mediate **inhibition** of (1H)-acetylcholine release from the isolated rat and guinea-pig trachea: Role of the airway mucosa and prostaglandins.
AUTHOR(S): Wessler, Ignaz [Reprint author]; Reinheimer, Torsten; Brunn, Gernot; **Anderson, Gary P.**; Maclagan, Jennifer; Racke, Kurt
CORPORATE SOURCE: Dep. Pharmacol., University Mainz, Obere Zahlbacher Strasse 67, D-55101 Mainz, Germany
SOURCE: British Journal of Pharmacology, (1994) Vol. 113, No. 4, pp. 1221-1230.
CODEN: BJPCBM. ISSN: 0007-1188.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Feb 1995
Last Updated on STN: 14 Mar 1995

AB 1. Rat or guinea pig isolated tracheae were labelled with (3H)-choline to measure evoked tritium outflow, which reflects neuronal release of (3H)-acetylcholine. Tritium outflow was evoked either by electrical stimulation of the extrinsic vagal nerve (rat tracheae) or by 27 mm

potassium (guinea pig tracheae). 2. In rat tracheae isoprenaline (0.01, 0.1 mu-M) **inhibited** evoked (3H)-acetylcholine release, whereas beta-2-adrenoceptor-selective agonists (fenoterol, formoterol, salbutamol) were ineffective. 3. The **inhibitory** effect of isoprenaline was abolished under the following conditions: (i) presence of propranolol (1 mu-M) or of the beta-1-selective antagonist CGP 20712 A (0.1 mu-M); (ii) removal of the mucosa at the start of the experiments; (iii) blockade of **cyclooxygenase** activity by 3 mu-M indomethacin. 4. In rat isolated tracheae prelabelled with (3H)-**arachidonic** acid, isoprenaline (0.1 mu-M) but not formoterol (0.01 mu-M) enhanced the outflow of (3H)-prostaglandins (PGD-2, PGE-2). This effect was blocked by 0.1 mu-M CGP 20712 A. 5. In guinea pig tracheae electrical stimulation of the extrinsic vagal nerve did not cause a constant release of (3H)-acetylcholine, but 27 mM potassium elicited a reproducible release of (3H)-acetylcholine. In this species both isoprenaline (0.1 mu-M) and formoterol (0.01 mu-M) **inhibited** evoked (3H)-acetylcholine release. **Inhibition** was abolished under the following conditions: (i) presence of propranolol (1 mu-M) or of the beta-2-selective antagonist ICI 118551 (0.3 mu-M); (ii) removal of the mucosa at the start of the experiments; (iii) blockade of **cyclooxygenase** activity by 3 mu-M indomethacin. 6. In conclusion, the present experiments have demonstrated that activation of beta-adrenoceptors localized in the mucosa mediates **inhibition** of (3H)-acetylcholine release from the neuroeffector junctions of the pulmonary, parasympathetic nerves most probably by the liberation of **inhibitory** prostaglandins from the airway mucosa. The adrenoceptor subtype involved differs in rat (beta-1 subtype) and guinea pig (beta-2 subtype) airways.

L204 ANSWER 20 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1993:413601 BIOSIS
DOCUMENT NUMBER: PREV199396079326
TITLE: Evaluation of 5-**lipoxygenase inhibitors**, zileuton, A-78773 and ICI-D-2138 in an ionophore (A-23187)-induced pleural inflammation model in the rat.
AUTHOR(S): Rao, Tadimeti S. [Reprint author]; Currie, Jerry L.; Shaffer, Alexander F.; **Isakson, Peter C.**
CORPORATE SOURCE: Searle Res. Dev., Mail Stop AA 5E, c/o Monsanto Co., 700 Chesterfield Pkwy North, St. Louis, MO 63198, USA
SOURCE: Life Sciences, (1993) Vol. 53, No. 9, pp. PL-147-PL-152. CODEN: LIFSAK. ISSN: 0024-3205.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Sep 1993
Last Updated on STN: 9 Sep 1993

AB Intrapleural injection of A-23187 (10 mu-g), a calcium ionophore, elicited rapid increase in biosynthesis of prostaglandins and leukotrienes in a time-dependent manner. 6-Keto-prostaglandin-F-1alpha (6-KPA) was the principal **cyclooxygenase** product with modest increases in levels of thromboxane B-2 and prostaglandin-E-2, Orally administered indomethacin, a selective **cyclooxygenase inhibitor**, and three selective 5-**lipoxygenase inhibitors**, zileuton, A-78773 and ICI-D-2138 markedly attenuated respective **arachidonate** pathways with projected ED-50 values of lt 1-2 mg/kg. Furthermore, a single oral administration of either ICI-D-2138 or A-78773 (each 20 mg/kg, po) resulted in persistent **inhibition** of 5-**lipoxygenase** pathway for up to 24 hr. These results indicate zileuton, A-78773 and ICI-D-2138 to be potent and selective **inhibitors** of 5-LO and document the utility of A-23187-induced pleural inflammation in evaluating efficacy of **inhibitors** of

arachidonic acid metabolism in vivo.

L204 ANSWER 21 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1990:513802 BIOSIS
DOCUMENT NUMBER: PREV199090131078; BA90:131078
TITLE: SIGNAL TRANSDUCTION BY THE PLATELET FC RECEPTOR.
AUTHOR(S): **ANDERSON G P** [Reprint author]; ANDERSON C L
CORPORATE SOURCE: DAVIS MED RES CENTER, ROOM 2054, 480 W 9TH AVE, COLUMBUS, OHIO 43210, USA
SOURCE: Blood, (1990) Vol. 76, No. 6, pp. 1165-1172.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 19 Nov 1990
Last Updated on STN: 20 Nov 1990

AB We have evaluated the mechanism by which crosslinking human platelet Fc receptor (FcR) for IgG triggers platelet aggregation and the platelet release reaction. Platelet FcR was crosslinked by incubating purified human platlets with anti-FcRII monoclonal antibody and F(ab')2 anti-mouse Ig. The resultant [Ca2+]i increase, monitored by Fura-2 and measured in the absence of extracellular Ca2+, reached a peak of 750 ± 50 nmol/L. The effects of **cyclooxygenase inhibitors**, aspirin and indomethacin, and a phospholipase A2 **inhibitor**, dibromoacetophenone, were examined. Regardless of the **inhibitor** , at least 25% of the [Ca2+]i increase remained. Thrombin (0.2 U/mL) stimulated an immediate [Ca2+]i increase that reached 1.95 ± 0.8 μmol/L . The [Ca2+]i increase generated by thrombin was only slightly reduced by these **inhibitors.** Crosslinking the FcRII of platelets resulted in a fivefold increase in the production of [3H]inositol phosphates, (IP) which, in the absence of extracellular Ca2+ was insensitive to aspirin. The activation of a [Ca2+]i increase along with the measured increases in IP indicate that FcRII crosslinking leads to the activation of phospholipase C (PLC). In contrast to thrombin, platelet activation via FcRII depends to a large extent on **arachidonic** acid metabolites. However, neither **cyclooxygenase** nor phospholipase A2 **inhibitors** completely blocked FcRII-stimulated [Ca2+]i increase. These observations led us to propose that crosslinking of platelet FcRII initially activates PLC.

L204 ANSWER 22 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1988:401052 BIOSIS
DOCUMENT NUMBER: PREV198886073691; BA86:73691
TITLE: **LIPOXYGENASE** METABOLITES MEDIATED INCREASED AIRWAYS RESPONSIVENESS TO HISTAMINE AFTER ACUTE PLATELET ACTIVATING FACTOR EXPOSURE IN THE GUINEA-PIG.
AUTHOR(S): **ANDERSON G P** [Reprint author]; FENNESSY M R
CORPORATE SOURCE: DEP PHARMACOL, UNIV MELBOURNE, PARKVILLE, VICTORIA 3052, AUSTRALIA
SOURCE: Agents and Actions, (1988) Vol. 24, No. 1-2, pp. 8-19.
CODEN: AGACBH. ISSN: 0065-4299.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 7 Sep 1988
Last Updated on STN: 7 Sep 1988

AB Platelet activating factor (Paf, 0.02 μg/kg, i.v. bolus) caused an acute increase in airways responsiveness to histamine in anaesthetized guinea-pigs prepared for recording airways resistance (RL) and dynamic

compliance (Cdyn). Aspirin pretreatment (10 mg/kg, i.v.) attenuated the return of airways responsiveness to prechallenge levels. Pretreatment with the combined **cyclooxygenase/lipoxygenase inhibitors** BW 755C (20 mg/kg, i.v.) and ETYA (20 mg/kg, i.v.), or with the putative cysteinyl-containing leukotriene antagonist FPL 55712 (0.25 mg/kg/min, i.v.), or a Paf antagonist SRI 63441 (2.5 mg/kg, i.v.), prevented Paf-induced increased airways responsiveness. **Inhibitors** of leukotriene synthesis, BW 755C and ETYA, or action, FPL 55712, had variable effects on Paf-induced bronchoconstriction. These data suggest that **lipoxygenase** metabolites, possibly leukotrienes, may mediate an acute increase in airways responsiveness to histamine after Paf exposure.

L204 ANSWER 23 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1988:401053 BIOSIS
DOCUMENT NUMBER: PREV198886073692; BA86:73692
TITLE: INCREASED AIRWAYS RESPONSIVENESS TO HISTAMINE INDUCED BY PLATELET ACTIVATING FACTOR IN THE GUINEA-PIG POSSIBLE ROLE OF **LIPOXYGENASE** METABOLITES.
AUTHOR(S): **ANDERSON G P** [Reprint author]; WHITE H L; FENNESSY M R
CORPORATE SOURCE: DEP PHARMACOL, UNIV MELBOURNE, PARKVILLE, VICTORIA 3052, AUSTRALIA
SOURCE: Agents and Actions, (1988) Vol. 24, No. 1-2, pp. 1-7. CODEN: AGACBH. ISSN: 0065-4299.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 7 Sep 1988
Last Updated on STN: 7 Sep 1988

AB In anaesthetized guinea-pigs pretreated with propronolol (1 mg/kg, i.v.), platelet activating factor (Paf, 0.02 μg/kg. i.v.) caused an acute increase in airways response to histamine (0.5-3.0 μ/kg, i.v.) measured as intratracheal pressure. Treatment with the **cyclooxygenase inhibitors**, aspirin (10 mg/kg, i.v.) or indomethacin (5 mg/kg, i.v.), enhanced the magnitude and duration of this effect but a combined **lipoxygenase/cyclooxygenase inhibitor**, BW 755C (20 mg/kg, i.v.), prevented the increase in responsiveness. In aspirin treated animals, a putative **lipoxygenase inhibitor** NDGA (10 mg/kg, i.v.), or atropine methyl nitrate (1 mg/kg, i.v.) or bilateral vagotomy reduced the magnitude of Paf-induced increased histamine responses but did not prevent the effect. Bronchoconstriction induced by Paf was variably influenced by the drug treatments. These data suggest that Paf causes an acute increase in airways responsiveness to histamine in the guinea-pig through a mechanism that may, in part, be dependent on the relase of **lipoxygenase** metabolites.

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